

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-978

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
		NDA NUMBER	
		21-978	
		NAME OF APPLICANT / NDA HOLDER	
		Connetics Corporation	

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)	
ACTIVE INGREDIENT(S) Desonide	STRENGTH(S) 0.05%
DOSAGE FORM Aerosol Foam	

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL			
a. United States Patent Number 6,730,288	b. Issue Date of Patent 5/4/2004	c. Expiration Date of Patent 9/8/2019	
d. Name of Patent Owner Connetics Australia Pty. Ltd.	Address (of Patent Owner) 8 Macro Court		
	City/State Rowville, Victoria		
	ZIP Code AUSTRALIA 3178	FAX Number (if available) fax: ++61 3 97630354	
	Telephone Number tel: ++61 3 97630022	E-Mail Address (if available)	
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Connetics Corporation	Address (of agent or representative named in 1.e.) 3160 Porter Drive		
	City/State Palo Alto, California		
	ZIP Code 94304	FAX Number (if available) 650.843.2802	
	Telephone Number 650.739.2614	E-Mail Address (if available)	

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☐ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☐ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2 Patent Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
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4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
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5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



OCT 2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Katrina J. Church, Executive Vice President, Legal Affairs, Connetics Corporation

Address

3160 Porter Drive

City/State

Palo Alto, CA

ZIP Code

94304

Telephone Number

650.739.2614

FAX Number (if available)

650.843.2802

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 21-978

SUPPL # N/A

HFD # 540

Trade Name

Generic Name Desonide Foam, 0.05%

Applicant Name Connetics Corporation

Approval Date, If Known September 19, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	17-426	Tridesilon (desonide) Ointment, 0.05%
NDA#	17-010	Tridesilon (desonide) Cream, 0.05%
NDA#	19-048	DESOWEN (desonide) Cream, 0.05%

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

N/A

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

DES.C.102, DES.C.101, DES.C.103, DES.C.104, DES.C.201, DES.C.202, DES.C.301

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 67,825 YES ☒ ! NO ☐
! Explain:

Investigation #2 !
!
IND # 67,825 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐

NO ☒

If yes, explain:

N/A

=====

Name of person completing form: Melinda Bauerlien

Title: Regulatory Project Manager

Date: September 14, 2006

Name of Office/Division Director signing form: Stanka Kukich, M.D.

Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Stanka Kukich
9/19/2006 04:27:53 PM

1.3.5.3 Statement of Claimed Exclusivity

In accordance with 21 CFR 314.108(b)(4), Connetics Corporation claims a three-year marketing exclusivity period for Desonide Foam, 0.05% (Desonide Foam) based on the following:

21 CFR 314.108(b)(4)(i):

This original New Drug Application (NDA) for Desonide Foam is submitted under section 505(b) of the Federal Food, Drug, & Cosmetic Act (the Act); specifically, this NDA is submitted under section 505(b)(1) of the Act;

21 CFR 314.108(b)(4)(ii):

The approval date of this NDA will be after 24 September 1984;

21 CFR 314.108(b)(4)(iii):

This NDA is for a drug product that contains an active moiety (desonide) that has been previously approved in another application under section 505(b) of the Act. Table 1 provides examples of drug products approved under section 505(b) of the Act which contain desonide as an active moiety:

Table 1: Examples of Desonide Drug Products Previously Approved Under Section 505(b) of the Act

NDA Number	Brand Name	Active Moiety	Year of Approval
17-426	Tridesilon (desonide) Ointment, 0.05%	desonide	1972
17-010	Tridesilon (desonide) Cream, 0.05%	desonide	1974
19-048	DESOWEN (desonide) Cream, 0.05%	desonide	1984

21 CFR 314.108(b)(4)(iv):

This NDA contains reports of new clinical investigations (other than bioavailability studies) conducted by Connetics Corporation that are essential to approval of this application. The studies required by FDA for approval of Desonide Foam, conducted by Connetics Corporation, and contained in this application are provided in Table 2. Connetics certifies that, to the best of its knowledge, the clinical studies listed in Table 2 met the definition of "new clinical investigation" as defined at 21 CFR 314.108(a).

Table 2: New Clinical Investigations Essential to Approval of Desonide Foam

Protocol Number	Study Type	Purpose of Clinical Investigation
<u>DES.C.102</u>	Vasoconstriction Pilot	(1) To validate vasoconstrictor assay precision. (2) To evaluate the vasoconstriction profile of Desonide Foam, 0.05%
<u>DES.C.101</u>	Vasoconstriction	Establish the bioavailability of Desonide Foam, 0.05% and establish assay sensitivity using potency of 1) Elocon [®] cream, 0.1%, 2) hydrocortisone cream 0.5%, 3) Tridesilon [®] cream, 0.05% and 4) Vehicle Foam.
<u>DES.C.103</u>	Sensitivity	Determine the allergic contact sensitization potential of Desonide Foam, 0.05%
<u>DES.C.104</u>	Skin Irritation	Evaluate the cutaneous irritation potential of Desonide Foam, 0.05%
<u>DES.C.201</u>	HPA Axis	To evaluate the safety of Desonide Foam, 0.05%, including its effect on the hypothalamic pituitary adrenal (HPA) axis
<u>DES.C.202</u>	Phase 2	Evaluate the safety and efficacy of Desonide Foam, 0.05% in the treatment of mild to moderate atopic dermatitis
<u>DES.C.301</u>	Phase 3	To evaluate the safety and efficacy of Desonide Foam, 0.05% in the treatment of mild to moderate atopic dermatitis and to demonstrate superior efficacy of Desonide Foam versus its vehicle

21 CFR 314.50(j)(4)(ii):

Connetics certifies that a thorough search of the scientific literature has been performed, and to the best of Connetics knowledge there are no published studies or publicly available reports of clinical investigations with Desonide Foam, 0.05% (Desonide Foam) for topical application in the treatment of atopic dermatitis. Therefore, it is Connetics' opinion that there are no publicly available reports that provide a sufficient basis for approval of Desonide Foam for the treatment of atopic dermatitis without reference to the new clinical investigation reports contained in this application.

21 CFR 314.50(j)(4)(iii):

Each study listed in Table 2 was submitted to Connetics IND 67,825 and Connetics was the sponsor identified on the FDA Forms 1571 submitted to the IND.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-978 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: November 21, 2005 Action Date: September 19, 2006

HFD 540 Trade and generic names/dosage form: (desonide) Foam, 0.05%

Applicant: Connetics Corporation Therapeutic Class: 3

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: atopic dermatitis

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

XNo: Please check all that apply: ☒ Partial Waiver ☐ Deferred ☒ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. 0 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. 3 yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- ☒ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☒ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. 3 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Regulatory Project Manager

cc: NDA 21-978
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Melinda Bauerlien
9/15/2006 07:54:22 AM

Denise Cook
9/19/2006 12:49:58 PM

Markham Luke
9/19/2006 12:53:06 PM
Concur

Stanka Kukich
9/19/2006 02:56:12 PM

1.9 PEDIATRIC USE INFORMATION

21 CFR 314.55 requires that "...each new application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective."

This NDA seeks approval of Desonide Foam, 0.05% (Desonide Foam) for the topical treatment of atopic dermatitis. The studies required by the FDA Division of Dermatologic and Dental Drug Products for approval and subsequently conducted by Connetics in support of this application included sufficient numbers of all pediatric subpopulations necessary to demonstrate safety and effectiveness of Desonide Foam in these populations, including subjects aged 3 months to 17 years of age. For example, the subject population for the pivotal Phase 3 safety and efficacy study DES.C.301 included the following age cohorts:

Cohort 1: ≥ 12 years < 18 years

Cohort 2: ≥ 6 years < 12 years

Cohort 3: ≥ 3 years < 6 years

Cohort 4: ≥ 3 months < 3 years

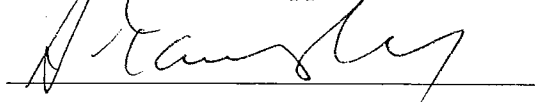
Efficacy was robustly established for all primary and secondary endpoints and Desonide Foam was safe and well-tolerated in this Phase 3 study. Comparable safety and efficacy was observed across all age groups. Consequently, Connetics does not propose age-related dose adjustments in the proposed Package Insert. The Final Study Report for Study DES.C.301 is located in Module 5, Section 5.3.5.1.2.

Additional clinical studies that enrolled pediatric subjects, including an HPA Axis suppression study, were performed to assess the safety of Desonide Foam. All clinical study reports supporting the safety and effectiveness of Desonide Foam for the pediatric population are provided in Module 5 of this application. Consequently, Connetics has satisfied the requirement at 21 CFR 314.55 to provide data adequate to assess the safety and effectiveness of Desonide Foam for the treatment of atopic dermatitis in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which Desonide Foam is safe and effective.

Debarment Certification

Clinical

Connetics Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

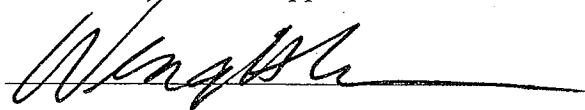


Alex Yaroshinsky, Ph.D.
Senior Director, Clinical Operations and Biostatistics

Date: 9/15/05

Nonclinical

Connetics Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

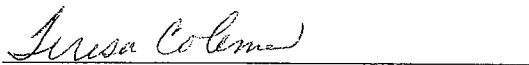


Wendy Chern, Ph.D.
Vice President, Research and Preclinical Development

Date: Sep 15, 2005

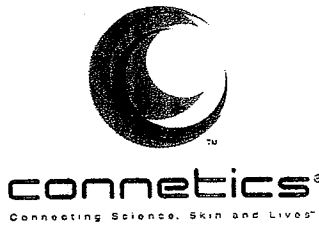
Quality

Connetics Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Teresa Coleman
Senior Director, Corporate Compliance

Date: 07 October 2005



September 11, 2006

Susan J. Walker, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and
Dental Drug Products (HFD-540)
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 21-978/A012
_____™ (desonide) Foam, 0.05%
Information Amendment: Response to Phase 4 Pharm/Tox Commitments

Attn: Melinda Bauerlien, M.S., Project Manager

Dear Dr. Walker:

Reference is made to the FDA fax of September 7, 2006 from Melinda Bauerlien (FDA) to Michael Eison (Connetics) containing FDA's proposed Phase 4 commitments for Pharm/Tox studies for _____™ (desonide) Foam, 0.05% (NDA 21-978).

With this submission, Connetics accepts the dates and milestones proposed by the Agency. A summary of the studies, milestones and dates are listed in the Submission Summary (attached). For reference, the FDA FAX of 07 September 2006 is attached.

This submission is provided in a PDF format on a CD-ROM with approximate size of 1 megabyte. The submission was scanned by Symantec AntiVirus Corporate Edition, Version 8.0, prior to submission. Connetics verifies that this electronic submission is virus free.

To expedite your receipt of this information, we also are faxing a hardcopy to 301.796.9895.

If the Division has any questions or needs further information regarding the content of this submission, you may contact me at telephone number 650.739.2688 or by e-mail at esmith@connetics.com, or Darlene O'Banion, Senior Manager, Regulatory Affairs, at 650.843.2829. The Regulatory Affairs facsimile number is 650.843.2802.

Sincerely,

Edward F. Smith III, Ph.D., R.A.C.
Sr. Director, Regulatory Affairs

SUBMISSION SUMMARY

Connetics agrees to conduct the following studies according to the following timelines.

1. The applicant commits to conducting a dermal carcinogenicity study with — (desonide) foam.

90-day dose ranging-finding study:	By April 1, 2008
Study protocol submission:	By October 1, 2008
Study start date:	By June 1, 2009
Final report submission:	By December 1, 2012

2. The applicant commits to conducting a study to determine the photoco-carcinogenic potential of — (desonide) foam.

90-day dose ranging-finding study:	By April 1, 2008
Study protocol submission:	By October 1, 2008
Study start date:	By June 1, 2009
Final report submission:	By December 1, 2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0338 Expiration Date: September 30, 2008 See OMB Statement on page 2.	
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, Parts 314 & 601)</i>		FOR FDA USE ONLY	
		APPLICATION NUMBER	

APPLICANT INFORMATION			
NAME OF APPLICANT Connetics Corporation		DATE OF SUBMISSION 11 September 2006	
TELEPHONE NO. (Include Area Code) 650-739-2688		FACSIMILE (FAX) Number (Include Area Code) 650-843-2802	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Connetics Corporation 3160 Porter Drive Palo Alto, CA 94304		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Not applicable	

PRODUCT DESCRIPTION			
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-978			
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Desonide, 0.05%		PROPRIETARY NAME (trade name) IF ANY Pending FDA Review	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) (11β, 16α)-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione			CODE NAME (If any) _____
DOSAGE FORM: Aerosol Foam	STRENGTHS: 0.05%	ROUTE OF ADMINISTRATION: Topical	
(PROPOSED) INDICATION(S) FOR USE: Atopic dermatitis			

APPLICATION DESCRIPTION			
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)			
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug <u>Not applicable</u> Holder of Approved Application <u>Not applicable</u>			
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO APENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER			
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: <u>Not applicable</u>			
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)			
REASON FOR SUBMISSION Amendment 012 in response to Agency request for information			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED <u>NA</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC			
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Not applicable for this submission.			
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) Not applicable for this submission.			

This application contains the following items: <i>(Check all that apply)</i>		
<input type="checkbox"/>	1. Index	
<input type="checkbox"/>	2. Labeling <i>(check one)</i> <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input type="checkbox"/>	4. Chemistry section	
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)	
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))	
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)	
<input checked="" type="checkbox"/>	20. OTHER <i>(Specify) Phase 4 Pharm/Tox commitments</i>	

CERTIFICATION

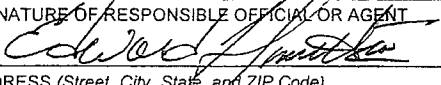
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Edward F. Smith III, Ph.D., Sr. Dir., Reg. Affairs	DATE: 11 September 2006
ADDRESS <i>(Street, City, State, and ZIP Code)</i> Connetics Corporation, 5160 Porter Drive, Palo Alto, CA 94304	Telephone Number (650) 739-2688	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266	Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448
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An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



September 8, 2006

Susan J. Walker, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and
Dental Drug Products (HFD-540)
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 21-978/A011
———TM (desonide) Foam, 0.05%
Information Amendment: Response to Proposed Draft Labeling

Attn: Melinda Bauerlien, M.S., Project Manager

Dear Dr. Walker:

Reference is made to the FDA fax of September 7, 2006 from Melinda Bauerlien (FDA) to Michael Eison (Connetics) containing FDA's latest proposal for draft labeling for ——— (desonide) Foam, 0.05% (NDA 21-978).

With this submission, Connetics accepts many of the FDA's editorial changes, requests that additional editorial changes be made to ensure consistency and correct spelling, and proposes one substantive change - an alternative approach to using the adverse event (AE) table to reflect observations of changes in blood pressure.

Connetics understands the Division's desire to reflect in the Package Insert observations made in the pivotal Phase 3 trial regarding changes in blood pressure, but does not agree that Table 1 (Commonly Occurring Adverse Events) is the appropriate place to do it. We note that the study investigators did not report these observations as AEs.

We propose instead that the following text be added to the ADVERSE REACTIONS section, as new text starting at the current line 226:

"Elevated blood pressure was observed in 6 (2%) subjects treated with ——— Foam and 1 (1%) subject ——— vehicle foam."

To facilitate the review of the changes proposed by Connetics, the following attachments are included:

- A table listing the changes proposed by Connetics, with an explanation of the changes (Attachment 1).
- Labeling with both FDA's and Connetics' changes accepted (Attachment 2).
- Labeling with Connetics' comments in "track-changes" (Attachment 3).

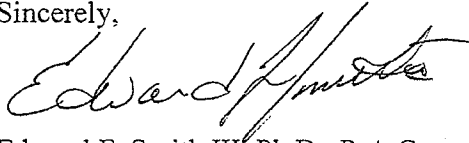
We note the Division proposes a teleconference early during the week of September 11-15. We would be happy to discuss these proposed Package Insert changes with you if after reviewing our proposals you believe there is still need for discussion. If the Division is comfortable with the changes we propose herein, we are prepared to accept the resulting Package Insert as final.

This submission is provided in a Word format on a CD-ROM with approximate size of 2 megabytes. The submission was scanned by Symantec AntiVirus Corporate Edition, Version 8.0, prior to submission. Connetics verifies that this electronic submission is virus free.

To expedite your receipt of this information, we also are faxing a hardcopy to 301.796.9895.

If the Division has any questions or needs further information regarding the content of this submission, you may contact me at telephone number 650.739.2688 or by email at esmith@connetics.com, or Darlene O'Banion, Senior Manager, Regulatory Affairs, at 650.843.2829. The Regulatory Affairs facsimile number is 650.843.2802.

Sincerely,



Edward F. Smith III, Ph.D., R.A.C.
Sr. Director, Regulatory Affairs



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: September 7, 2006

To: Michael Eison	From: Melinda Bauerlien, M.S. Project Manager
Company: Connetics	Division of Dermatology & Dental Products
Fax number: (650) 843-2802	Fax number: (301) 796-9895
Phone number: (650) 739-2614	Phone number: (301) 796-2110
Subject: NDA 21-978 Phase 4 commitments	

Total no. of pages including cover: 3

Comments: Following are the requested Phase 4 commitments for Pharm/Tox. If you agree to these commitments please send in a formal submission stating the commitments and that you agree to them.

Document to be mailed: ☐ YES ☒ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

1. The applicant commits to conducting a dermal carcinogenicity study with _____
(desonide) foam.

90-day dose range-finding study:	By April 1, 2008
Study protocol submission:	By October 1, 2008
Study start date:	By June 1, 2009
Final report submission:	By December 1, 2012

2. The applicant commits to conducting a study to determine the photoco-carcinogenic potential of _____ (desonide) foam.

90-day dose range-finding study:	By April 1, 2008
Study protocol submission:	By October 1, 2008
Study start date:	By June 1, 2009
Final report submission:	By December 1, 2011

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Melinda Bauerlien
9/7/2005 01:39:32 PM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: September 6, 2006

To: Michael Eison	From: Melinda Bauerlien, M.S. Project Manager
Company: Connetics	Division of Dermatology & Dental Products
Fax number: (650) 843-2802	Fax number: (301) 796-9895
Phone number: (650) 739-2614	Phone number: (301) 796-2110
Subject: NDA 21-978	

Total no. of pages including cover: 24

Comments: 7/11/06 tcon minutes provided

Document to be mailed: ☐ YES ☒ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

MEMORANDUM OF TELECON

DATE: 7/11/06, 1:30 P.M.

APPLICATION NUMBER: NDA 21-978

DRUG PRODUCT: (desonide) Foam, 0.05%

BETWEEN:

Name: Lincoln Krochmal, M.D., Executive Vice President, Research and Product Development
Nandan Oza, Vice President, Manufacturing and Supply Chain Operations
David Dimmick, Vice President, Quality and Compliance
John Statler, Ph.D., Senior Director, Analytical Technical Operations
Luis Pena, Vice President, Project Management
Matt Foehr, Senior Vice President, Technical Operations
Melody Wyres, Director, Clinical Operations
Aaron Potts, Manager, Clinical Operations
Bill Schaber, Senior Director, Quality Assurance
Doris Boesch, Stability Program Director
Mark Buggy, Senior Manager, Contract Manufacturing Operations
Rebecca Mock, Associate Director, Regulatory Affairs

Representing: Connetics Corporation

AND

Name: Brian Rogers, Manufacturing Scientist, ONDQA
Gene Holbert, CMC Reviewer, ONDQA
Shulin Ding, Pharmaceutical Assessment Lead, ONDQA
Denise Cook, Clinical Reviewer, Dermatology, DDDP
Markham Luke, Clinical Team Leader, Dermatology, DDDP
Linda Athey, Project Manager, ONDQA
Melinda Bauerlien, M.S., Regulatory Project Manager, DDDP

SUBJECT: NDA 21-978

The teleconference was requested by the Agency to request specific information from the sponsor concerning the submitted NDA. An Information Request was sent to the sponsor on April 12, 2006 and a response was received in May of 2006.

1. The Agency wants to know the effect of can pressure on the foam volume and whether the volume is variable or constant at different pressures. The volume is important because patients tend to judge how much product they are getting based on the size of foam. The patients may spray more than what they should if the foam volume is small due to a low pressure.

2. The sponsor needs to explain why they set a broad drug product specification on the can pressure. The to-be-marketed drug product should be identical to that used in the Phase 3 studies. The proposed acceptance criterion for can pressure for commercial batches is no less than —psi which is much broader than what was actually used in the Phase 3 studies (between —psi).

The sponsor stated that the product used in the Phase 3 trials was identical to the product that would be sold. The initial specification had not changed. -They asked what kind of information the Agency was looking for in order to support their statement.

The Agency replied that they needed to provide the foam density or the volume of foam that was dispensed per mass of desonide. The Agency wanted data from 20, 30 and 40 psi on volume of foam expelled. If this piece of information was not provided, the Agency would ask for tighter controls on pressure. The Agency wanted to ensure that foam density stayed the same at different pressures.

The sponsor stated that they could tighten release and stability specifications to NLT — psi and propose a wider specification post approval.

The Agency agreed with the sponsor's proposal and the revised specification of no less than — psi.

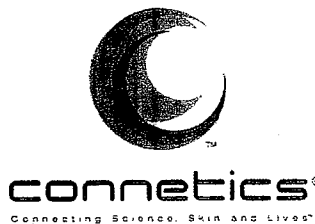
The conversation ended amicably.

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this page is the manifestation of the electronic signature.**

/s/

Melinda Bauerlien
8/24/2006 01:35:43 PM
CSO

Shulin Ding
8/24/2006 06:36:50 PM
CHEMIST



August 29, 2006

Susan J. Walker, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and
Dental Drug Products (HFD-540)
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: Desonide Foam, 0.05% NDA 21-978/A010
Chemistry, Manufacturing, and Controls (CMC) Response to Information Request
Letter Dated August 28, 2006

ATTN: Ms. Linda Mullins Athey, Regulatory Health Project Manager for Quality

Dear Dr. Walker,

In accordance with 21 CFR 314.60, Connetics Corporation (Connetics) is amending NDA 21-978 for Desonide Foam 0.05% —, in response to the Agency's information request letter dated 28 August 2006. Please refer to the Submission Summary for a detailed description of the amendment.

The amendment is being submitted in electronic format. Connetics certifies that this electronic submission is virus-free. The submission is 1 MB and was scanned by Symantec Antivirus Corporate Edition version 8.0 prior to submission.

Connetics has provided copies of the cover letter to the affected District Offices. Connetics can provide copies of this amendment to District Offices upon request.

If you have any questions regarding this submission, please call me at (650) 739-2614 or Rebecca Mock, Associate Director, Regulatory Affairs at (650) 739-2979. The Regulatory Affairs facsimile number is (650) 843-2802.

Sincerely,

Michael S. Eison, Ph.D.
Vice President, Regulatory Affairs

cc: San Francisco District Office (cover letter only)
Dallas District Office (cover letter only)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-978

INFORMATION REQUEST LETTER

Connetics Corporation
Attention: Michael S. Eison,
Vice President, Regulatory Affairs
3160 Porter Dr.
Palo Alto, CA 94304

Dear Dr. Eison

Please refer to your November 18, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Desonide Foam, 0.05%.

We also refer to your submission dated March 15, May 2, May 24 and July 18, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and request for additional information. We request a prompt written response in order to continue our evaluation of your NDA.

Please amend your Comparability Protocols as follows:

Qualification of an Alternate Manufacturing Site for the Manufacture of Desonide Foam

Item 5, Data and Information to be Reported, please add:

- e. Certification that the facility is within 2 years of a satisfactory inspection

Comparability Protocol for Additional Product Sizes of

and

Comparability Protocol for New Product Size ~~Approved 100 g Size~~

Item 5, Data and Information to be Reported, please revise as follows:

- a. A comparison of the new packaging components with those approved in this NDA;
- b. A comparison of the specifications for the new size with that approved in this NDA;
- c. Comparative dispensing rates for initial, middle and last portion of each size can;
- d. Three months long term and accelerated stability data; and
- e. Labeling.

If you have any questions, call Linda Mullins Athey, Regulatory Health Project Manager for Quality, at 301-796-2096.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Moo-Jhong Rhee
8/28/2006 02:20:53 PM



August 24, 2006

Susan J. Walker, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and
Dental Drug Products (HFD-540)
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 21-978/A009
Response to FDA-Desonide Foam, 0.05% Request for Information

Attn: Melinda Bauerlien, M.S., Project Manager

Dear Dr. Walker:

Reference is made to the FDA fax to Connetics dated 17 August 2006, containing the proposed labeling for ~~_____~~TM (desonide) Foam, 0.05%.

As requested by the Agency, Connetics is submitting its response to the proposed ~~_____~~ Foam labeling. To facilitate the review of the changes proposed by Connetics, the following attachments are included:

- Labeling with FDA's "track-changes" comments accepted, including Connetics' comments in "track-changes" (Attachment 1).
- Labeling with both FDA's and Connetics' changes accepted (Attachment 2).
- A table listing the changes proposed by Connetics, with an explanation of the changes (Attachment 3).
- An example of a ~~_____~~ (desonide) Foam, 0.05% 100 g can label, consistent with the revisions suggested by FDA in the labeling (refer to lines 257-262 - Attachment 4).

This submission is provided in a Word format on a CD-ROM with approximate size of 2 megabytes. The submission was scanned by Symantec AntiVirus Corporate Edition, Version 8.0, prior to submission. Connetics verifies that this electronic submission is virus free.

To expedite your receipt of this information, we also are faxing a hardcopy to 301.796.9895.

If the Division has any questions or needs further information regarding the content of this submission, you may contact me at telephone number 650.739.2688 or by email at

submission, you may contact me at telephone number 650.739.2688 or by email at

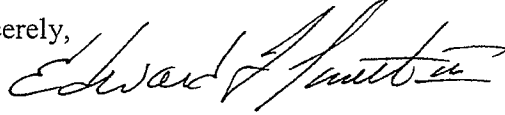
submission, you may contact me at telephone number 650.739.2688 or by email at

August 24, 2006
Page 2 of 2

Connetics Confidential

esmith@connetics.com, or Darlene O'Banion, Senior Manager, Regulatory Affairs, at 650.843.2829. The Regulatory Affairs facsimile number is 650.843.2802.

Sincerely,

A handwritten signature in cursive script, appearing to read "Edward F. Smith III".

Edward F. Smith III, Ph.D., R.A.C.
Sr. Director, Regulatory Affairs



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: August 17, 2006

To: Michael Eison	From: Melinda Bauerlien, M.S. Project Manager
Company: Connetics	Division of Dermatology & Dental Products
Fax number: (650) 843-2802	Fax number: (301) 796-9895
Phone number: (650) 739-2614	Phone number: (301) 796-2110
Subject: NDA 21-978 request for information	

Total no. of pages including cover: 2

Comments: Please provide the following information as soon as possible

In the information submitted on August 15, 2006 as Table 1, please include 2 columns indicating age and % BSA affected of each patient. Also, please identify the patients who demonstrated HPA axis suppression.

Document to be mailed: ☐ YES ☒ NO

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August 22, 2006

Susan J. Walker, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and
Dental Drug Products (HFD-540)
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 21-978/A008
Response to FDA Desonide Foam, 0.05% Request for Information

Attn: Melinda Bauerlien, M.S., Project Manager

Dear Dr. Walker:

Reference is made to the FDA fax to Connetics dated 17 August 2006. Further reference is made to the FDA fax to Connetics dated 14 August 2006, and Connetics response dated 15 August 2006, submitted by Fax and electronically (NDA 21-978/A007).

Connetics is providing a response with additional information requested with regard to age, % BSA affected of each patient, and to identify the patients who demonstrated HPA axis suppression.

Please find with this submission an updated table providing for each subject enrolled in Study DES.C.201 the age at Baseline, % BSA involvement at Baseline, the total amount of study drug used, the number of days on treatment, the mean amount of study drug used per day and if HPA suppression was present at Week 4.

The reviewer is directed to the appropriate datasets submitted in the NDA from which several of the values presented herein were derived.

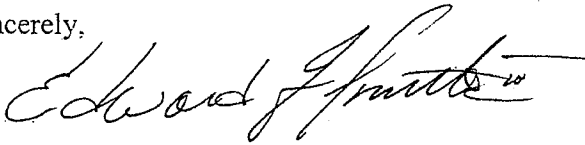
Connetics believes that this information adequately addresses the reviewer's request.

This submission is provided in a Word format on a CD-ROM with approximate size of 2 megabytes. The submission was scanned by Symantec AntiVirus Corporate Edition, Version 8.0, prior to submission. Connetics verifies that this electronic submission is virus free.

To expedite your receipt of this information, we also are faxing a hardcopy to 301.796.9895.

If the Division has any questions or needs further information regarding the content of this submission, you may contact me at telephone number 650.739.2688 or by email at esmith@connetics.com, or Darlene O'Banion, Senior Manager, Regulatory Affairs, at 650.843.2829. The Regulatory Affairs facsimile number is 650.843.2802.

Sincerely,

A handwritten signature in cursive script, reading "Edward F. Smith III". The signature is written in dark ink and includes a stylized flourish at the end.

Edward F. Smith III, Ph.D., R.A.C.
Sr. Director, Regulatory Affairs

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/s/

Melinda Bauerlien
8/17/2006 01:42:49 PM
CSO



August 15, 2006

Susan J. Walker, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and
Dental Drug Products (HFD-540)
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 21-978/A007
Request for Information

Attn: Melinda Bauerlien, M.S., Project Manager

Reference is made to the FDA fax to Connetics dated August 14, 2006 requesting by August 16, 2006 at 12:00 Noon EST a response to an NDA reviewer's question.

The purpose of this submission is to provide the requested information with regard to how much Desonide Foam, 0.05% was applied to each subject at each application in Study DES.C.201.

Please find with this submission a table providing, by patient, the total amount (grams) of drug used during the conduct of this study, and, for each patient, the mean daily amount of drug used (grams/day). We also note in this submission that the mean percent body surface area (% BSA) of involvement at baseline for subjects in this study (38.5%) exceeded the inclusion criteria (% BSA > 25%) for this study and exceeded the % BSA of involvement of the mild to moderate atopic dermatitis population (21.3%) treated with Desonide Foam in the pivotal Phase 3 trial (DES.C.301) supporting this NDA. On average, the BSA to which Desonide Foam was applied in subjects in the DES.C.201 HPA axis study was 80% greater than the treated BSA in the pivotal DES.C.301 study.

In DES.C.201, all treatments were administered twice a day for 4 weeks and subjects were instructed to continue to apply study drug to cover at least 25% treatable BSA for 4 weeks regardless of improvement or clearing of disease.

The reviewer is directed to the appropriate dataset submitted in the NDA from which several of the values presented herein were derived.


Connetics believes that this information reflects that Study DES.C.201 was conducted under maximal use conditions, and trusts this adequately addresses the reviewer's question.

This submission is provided in a CD-ROM format with approximate size of 2 megabytes. The submission was scanned by Symantec AntiVirus Corporate Edition, Version 8.0, prior to submission. Connetics verifies that this electronic submission is virus free.

To expedite your receipt of this information, we also are faxing a hardcopy to 301.796.9895.

We trust that this reply addresses your concerns. If you have any questions or comments about this submission, please contact me at 650.739.2614 or Darlene O'Banion, Senior Manager, Regulatory Affairs, at 650.843.2829. The Regulatory Affairs facsimile number is 650.843.2802.

Sincerely,

A handwritten signature in black ink, appearing to read "Michael S. Eison". The signature is fluid and cursive, with a long horizontal stroke at the end.

Michael S. Eison, Ph.D.
Vice President, Regulatory Affairs



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: August 14, 2006

To: Michael Eison	From: Melinda Bauerlien, M.S. Project Manager
Company: Connetics	Division of Dermatology & Dental Products
Fax number: (650) 843-2802	Fax number: (301) 796-9895
Phone number: (650) 739-2614	Phone number: (301) 796-2110
Subject: NDA 21-978 request for information	

Total no. of pages including cover: 2

Comments: Please provide the following information by Wednesday 8/16 at 12 noon:

Please submit information (or direct us to the proper section of their submission) on the amount of formulation applied to each patient during each application in Study DES.C.201.

Document to be mailed: ☐ YES ☒ NO

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/s/

Melinda Bauerlien
8/14/2006 01:55:14 PM
CSO

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; HFD-420)**

DATE RECEIVED: August 10, 2006	DESIRED COMPLETION DATE: December 9, 2005	OSE REVIEW #: 05-0103-2
DATE OF DOCUMENT: November 9, 2005	PDUFA DATE: September 21, 2006	

TO: Susan J. Walker, M.D.
Director, Division of Dermatology and Dental Products
HFD-540

THROUGH: Alina Mahmud, R.Ph., MS, Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Tselaine Jones Smith, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME:
Verdeso™
(Desonide Foam) 0.05%

NDA SPONSOR: Connetics Corporation

NDA #: 21-978

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Verdeso. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Verdeso, acceptable from a promotional perspective.
4. The Division and the CMC/Branch Chief recommended that the sponsor use CDER's manuscript entitled "Topical drug classification" authored by Lucinda Buhse and published in the *International Journal of Pharmaceutics* 295 (2005) pp. 101-112 for guidance. This contradicts the recommendation made by Dr. Guirag Poochikian that the established name should be "Drug Topical Aerosol". Therefore, DMETS recommends that the Division contact Dr. Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee, for clarification of the established name as outlined in Section III of this review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.



July 24, 2006

Susan J. Walker, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and
Dental Drug Products (HFD-540)
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 21-978/A006
Request for Information

Attn: Melinda Bauerlien, M.S., Project Manager

Reference is made to the FDA fax of July 11, 2006 requesting additional information with regard to subjects in study DES.C.301 who had abnormal blood pressures ($> 140/90$, including either isolated systolic or diastolic pressures).

The purpose of this submission is to provide the requested information. In this response to the Request for Information, FDA's question is provided in bold text, followed by Connetics' reply.

After carefully assessing the information available for subjects in study DES.C.301 with reports of abnormal blood pressures, Connetics (like its investigators) concludes that these alterations in blood pressure were not of clinical significance, and that no clear relationship between elevations of blood pressure and study drug could be established.

This submission is provided in a CD-ROM format with approximate size of 2 megabytes. The submission was scanned by Symantec AntiVirus Corporate Edition, Version 8.0, prior to submission. Connetics verifies that this electronic submission is virus free.

To expedite your receipt of this information, we also are faxing a hardcopy to 301.796.9895.

We trust that this reply addresses your concerns. If you have any questions or comments about this submission, please contact me at 650.739.2614 or Darlene O'Banion, Senior Manager, Regulatory Affairs, at 650.843.2829. The Regulatory Affairs facsimile number is 650.843.2802.

Sincerely,

Michael S. Eison, Ph.D.
Vice President, Regulatory Affairs



July 18, 2006

Susan J. Walker, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and
Dental Drug Products (HFD-540)
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: Desonide Foam, 0.05% NDA 21-978/A005
Chemistry, Manufacturing, and Controls (CMC) and Revised Labeling Amendment:
Response to FDA Request

ATTN: Ms. Melinda Bauerlien, MS, Regulatory Project Manager

Dear Dr. Walker,

In accordance with 21 CFR 314.60, Connetics Corporation (Connetics) is amending the unapproved NDA 21-978 for Desonide Foam 0.05% (—) in response to the Agency's request as discussed at the 11 July 2006 teleconference. Please refer to the Submission Summary for a detailed description of the amendment.

The amendment is being submitted in electronic format. The SPL and Microsoft Word version of the revised label are included. Connetics certifies that this electronic submission is virus-free. The submission is 1 MB and was scanned by Symantec Antivirus Corporate Edition version 8.0 prior to submission.

Connetics has provided copies of the cover letter to the affected District Offices. Connetics can provide copies of this amendment to District Offices upon request.

If you have any questions regarding this submission, please call me at 650.739.2614 or Rebecca Mock, Associate Director, Regulatory Affairs at 650.739.2979. The Regulatory Affairs facsimile number is 650.843.2802.

Sincerely,

Michael S. Eison, Ph.D.
Vice President, Regulatory Affairs

cc: San Francisco District Office (cover letter only)
Dallas District Office (cover letter only)



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: July 11, 2006

To: Michael Eison	From: Melinda Bauerlien, M.S. Project Manager
Company: Connetics	Division of Dermatology & Dental Products
Fax number: (650) 843-2802	Fax number: (301) 796-9895
Phone number: (650) 739-2614	Phone number: (301) 796-2110
Subject: NDA 21-978 request for information	

Total no. of pages including cover: 2

Comments: Please provide the following information as soon as possible:

The sponsor should provide a summary table of all subjects in study DES.C.301 who had abnormal blood pressures, >140/90, either isolated systolic or diastolic should also be included. The table should include the ages of the patients and any concomitant medical conditions that could explain the abnormality. Provide whether there was a repeat or follow-up of the blood pressure to see if it returned to normal. If not, was there a referral to a primary care doctor. A summary should be provided for each patient. The sponsor is referred to their tables 51 and 52 which provides summaries of BP but no details. If this information is already included in the NDA, the please identify where it can be found.

Document to be mailed: ☐ YES ☒ NO

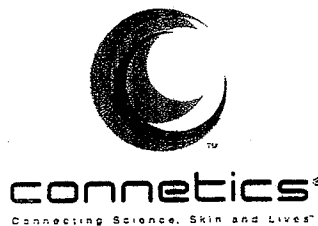
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ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL,
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/s/

Melinda Bauerlien
7/11/2006 09:47:45 AM
CSO



May 24, 2006

Stanka Kukich, MD, Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and
Dental Drug Products (HFD-540)
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: Desonide Foam, 0.05% NDA 21-978/A004
Chemistry, Manufacturing, and Controls (CMC) Amendment: Response to FDA
Comments

ATTN: Ms. Maria Anderson, Regulatory Project Manager

Dear Dr. Kukich,

Connetics Corporation (Connetics) is amending NDA 21-978 with this response to the CMC Information Request received in the fax dated April 26, 2006, a copy of which is provided in Attachment 1.

The amendment is being submitted in electronic format. Connetics certifies that this electronic submission is virus-free. The submission is 4 MB and was scanned by Symantec Antivirus Corporate Edition version 8.0 prior to submission.

Reference is made to Guidance for Industry—Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, Section K, which states “FDA district offices have access to documents submitted in electronic format. Therefore, when sending submissions in electronic format you need not provide any documentation to the FDA Office of Regulatory Affairs District Office.”

Accordingly, Connetics has not provided separate copies of any part of this application to the affected District Offices. However, Connetics can provide copies of technical sections of this application to District Offices upon request.

Connetics Confidential
May 24, 2006
Page 2 of 2

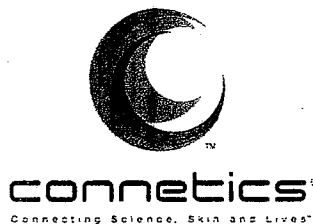
If you have any questions regarding this submission, please call me at 650.739.2614 or Rebecca Mock, Associate Director, Regulatory Affairs at 650.739.2979. The Regulatory Affairs facsimile number is 650.843.2802.

Sincerely,

A handwritten signature in black ink, appearing to read "Michael S. Eison". The signature is fluid and cursive, with the first name "Michael" being the most prominent part.

Michael S. Eison, Ph.D.
Vice President, Regulatory Affairs

cc: San Francisco District Office (cover letter only)
Dallas District Office (cover letter only)



11 May 2006

Stanka Kukich, MD, Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic &
Dental Drug Products (HFD-540)
5901-B Ammendale
Beltsville, MD 20705-1266

**RE: NDA 21-978/Amendment 003
Desonide Foam, 0.05%
New Patent Information**

Attention: Maria Anderson, Regulatory Project Manager

Dear Dr. Kukich,

In accordance with 21 CFR 314.53(c)(2)(ii) and 21 CFR 314.53(d)(1) Connetics Corporation (Connetics) is amending the unapproved application for Desonide Foam, 0.05% (Desonide Foam), NDA 21-978, to submit information for a new Connetics' patent, US Patent Number 7,029,659 B2.

This amendment is electronically submitted in accordance with Guidance for Industry - Providing Regulatory Submissions in Electronic Format - NDAs (January 1999). Connetics is also providing a hard copy of this amendment because it contains an original signature document identical to that provided in the electronic submission.

This amendment is provided in a CD-ROM format, with an approximate size of 1 MB. The submission was scanned by Symantec Antivirus Corporate Edition, Version 8.0, prior to submission. Connetics verifies that this electronic submission is virus-free.

If you have any questions or comments about this amendment, please contact me at (650) 739-2614 or Darlene O'Banion, Senior Manager, Regulatory Affairs at (650) 843-2829. The Regulatory Affairs facsimile number is (650) 843-2802.

Sincerely,

Darlene O'Banion for Michael Eison

Michael S. Eison, PhD
Vice President, Regulatory Affairs



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 1, 2006

To: Michael S. Eison, Ph.D.	From: Maria M. Anderson, B.S.N. Regulatory Project Manager
Company: Connetics	Division of Dermatology & Dental Products
Fax number: (650) 843-2802	Fax number: (301) 796-9894 or -9895
Phone number: (650) 739-2614	Phone number: (301) 796-1880
Subject: NDA 21-978	

Total no. of pages including cover:

2

Request from CMC:

Please send three units of the product. The samples can be aged but not expired. Please have the samples sent ASAP to:

Maria M. Anderson (**DESK COPY**)

WO-22, Rm. 5175, HFD-40

10903 New Hampshire Ave.

Silver Spring, MD 20993

Document to be mailed:

☐ YES

☒ NO

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/s/

Maria Anderson
5/1/2006 07:57:23 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: April 26, 2006

To: Michael S. Eison, Ph.D.	From: Maria M. Anderson, B.S.N. Regulatory Project Manager
Company: Connetics	Division of Dermatology & Dental Products
Fax number: (650) 843-2802	Fax number: (301) 796-9894 or -9895
Phone number: (650) 739-2614	Phone number: (301) 796-1880
Subject: NDA 21-978	

Total no. of pages including cover: 5

Comments: Please respond by May 26, 2006. Send response via facsimile and send an official copy to the main document room. Thanks.

Document to be mailed: ☐ YES ☒ NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

INFORMATION REQUEST

In connection with our review of the Chemistry Manufacturing and Control (CMC) sections of your NDA 21-978 for Desonide Foam 0.05%, submitted on Nov. 18, 2005, we have the following comments and requests for information:

1. Please clarify what the commercial batch size will be.
2. Please provide a table comparing the equipment used to produce the clinical/stability batches to the equipment proposed for commercial production.
3. Please explain the purpose of _____
4. Please clarify the following statement found in the Linearity and Range section of the method validation: "_____

5. We note that the product is labeled to be shaken before use. Does this mean that the phases separate in the container or is this just to redistribute the propellant? Please indicate how long the containers need to be shaken.
6. Please provide data to demonstrate that the emulsion does not phase separate on standing throughout the shelf life of the product.
7. Please indicate the position of the lot number and expiration date on the container and carton labels.
8. You have proposed an acceptance criterion of not less than _____psi for pressure. Is that pressure sufficient to ensure the quality of the foam when the can is nearly empty? Data from the stability batches suggests that the pressure criterion could be increased to not less than _____psi.
9. The following comments result from comparison of the submitted executed batch record and the manufacturing description.
 - a. _____

2 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Maria Anderson
4/26/2006 01:01:58 PM
CSO



March 15, 2006

Stanka Kukich, MD, Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and
Dental Drug Products (HFD-540)
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: Desonide Foam, 0.05% NDA 21-978/A001
120-Day Safety Update
Chemistry, Manufacturing, and Controls (CMC) Amendment: Response to FDA
Comments and Drug Product Stability Update

ATTN: Ms. Maria Anderson, Regulatory Project Manager

Dear Ms. Kukich,

Connetics Corporation (Connetics) is amending NDA 21-978 with this 120-day safety update in accordance with 21 CFR 314.50(d)(5)(vi)(b). There is no new safety information to report.

Consistent with agreements reached at the 12 September 2005 Pre-NDA meeting and requests made in the 31 January 2006 filing communication, CMC information is being provided to respond to FDA comments and to update drug product stability. Please see attached submission summary for CMC information.

The amendment is being submitted in electronic format. Connetics certifies that this electronic submission is virus-free. The submission is 3 MB and was scanned by Symantec AntiVirus Corporate Edition version 8.0 prior to submission.

Reference is made to Guidance for Industry—Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, Section K, which states “FDA district offices have access to documents submitted in electronic format. Therefore, when sending submissions in electronic format you need not provide any documentation to the FDA Office of Regulatory Affairs District Office.”

Accordingly, Connetics has not provided separate copies of any part of this application to the affected District Offices. However, Connetics can provide copies of technical sections of this application to District Offices upon request.

If you have any questions regarding this submission, please call me at 650.739.2614 or Rebecca Mock, Associate Director, Regulatory Affairs at 650.739.2979. The Regulatory Affairs facsimile number is 650.843.2802.

Sincerely,

A handwritten signature in cursive script, appearing to read "Michael S. Eison".

Michael S. Eison, Ph.D.
Vice President, Regulatory Affairs

cc San Francisco District Office (cover letter only)
Dallas District Office (cover letter only)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-978

Connetics Corporation
Attention: Michael S. Eison, Vice President, Regulatory Affairs
3160 Porter Dr.
Palo Alto, CA 94304

Dear Dr. Eison

Please refer to your November 18, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Desonide Foam, 0.05%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on January 20, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Chemistry and Manufacturing Controls:

A statement regarding the readiness for inspection and CFN numbers for drug substance facilities were not provided.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

Chemistry and Manufacturing Controls:

Please provide a statement regarding the readiness for inspection for drug substance manufacturer and testing laboratories, and provide CFN numbers for the facilities.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 21-978

Page 2

If you have any questions, call Maria M. Anderson, Regulatory Project Manager, at (301) 796-2110.

Sincerely yours,

{See appended electronic signature page}

Stanka Kukich, M.D.
Acting Division Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Stanka Kukich
1/31/2006 03:02:04 PM

Division of Dermatologic and Dental Drug Products (HFD-540)
Pharmacology/Toxicology Checklist for NDA Filing Meeting

Date: 12-28-05
Reviewer: Barbara Hill
NDA Number: 21-978
Drug Name: _____ (desonide) foam, 0.05%
CAS Number: 638-94-8
Drug Type: 3S
Drug Class: Corticosteroid
Indication: Corticosteroid responsive dermatoses
Route of Administration: Topical
Date CDER Received: 11-21-05
User Fee Date: 9-21-05
Date of Draft Review: 6-15-05
Sponsor: Connetics Corporation, Palo Alto, CA

Fileability:

On initial overview of the NDA application:

- (1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner to allow a substantive review to be completed? YES

This is a totally electronic eCTD NDA submission.

- (2) Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner to enable a timely and substantive review? YES

- (3) Is the pharmacology/toxicology section of the NDA sufficiently legible to permit a substantive review to be completed? YES

- (4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute studies*, chronic studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? YES

The sponsor stated in the pre-NDA briefing package that they intend to study desonide foam in a 2-year dermal carcinogenicity study in a single species and a photocarcinogenicity study in a single species as a post-marketing commitment. During the pre-NDA meeting, the Division requested that the Sponsor include a timeline for conduct of both nonclinical post-marketing commitments in the desonide foam NDA submission.

The sponsor states in the NDA submission that they plan to conduct a dermal carcinogenicity study in a single species and a photocarcinogenicity study in a single species, with Desonide Foam as a post-marketing commitment. The sponsor further states that the dose-ranging studies will be initiated within 1 year of the product launch of Desonide Foam in the US market, and the protocols for the definitive studies will be submitted to the CAC within 1 year after completion of the dose-ranging studies. The adequacy of this timeline is a review issue.

- (5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the Sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required? N/A
- (6) Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either mg/m² or comparative serum/plasma levels) and in accordance with 201.57? YES
- (7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? YES

It was requested during the pre-NDA meeting that the sponsor provide safety data to support the level of leachables (i.e., _____) contained in the desonide foam drug product in the NDA submission. The sponsor has included a document titled "Risk assessment of _____ as potential leachable impurities in a topical pharmaceutical product" in the NDA submission. It is review issue to determine whether the submitted information is adequate or not.

It was requested during the pre-NDA meeting that the sponsor provide the level of _____ butadiene in the propane /butane propellant used for the desonide foam drug product as mole% to determine if the level was low enough to not pose a cancer risk. The sponsor has provided information in the NDA submission that indicates that the level of _____ in the propane /butane propellant used for the desonide foam drug product is less than _____ mole%, which has been previously determined as acceptable.

- (8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor submitted a rationale to justify the alternative route? YES
- (9) Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? YES

- | | | |
|------|--|-----|
| (10) | Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics? | N/A |
| (11) | Has the Sponsor <u>submitted</u> a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? | YES |
| (12) | From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. | YES |
| (13) | If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify: | NO |
| (14) | Issues that should not be conveyed to the Sponsor: | N/A |

Pharmacology Reviewer

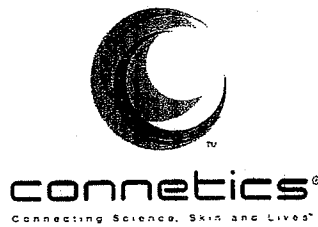
Pharmacology Supervisor

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Barbara Hill
1/5/2006 11:15:50 AM
PHARMACOLOGIST

Paul Brown
1/5/2006 02:37:20 PM
PHARMACOLOGIST



November 18, 2005

Ms. Stanka Kukich, MD, Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and
Dental Drug Products
5901-B Ammendale Road
Beltsville, MD 20855

RE: **NDA 21-978 - Desonide Foam, 0.05%**
Original NDA Submission
Indication: Atopic Dermatitis

Dear Ms.

ATTN: Ms. Felecia Curtis, Regulatory Project Manager

Dear Ms. Kukich,

In accordance with 21 CFR 314, this is an original New Drug Application (NDA) submission for Desonide Foam, 0.05% (Desonide Foam) for the treatment of atopic dermatitis. This NDA is being filed under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The clinical studies supporting this NDA were conducted under IND 67,825.

User Fee

In accordance with the FD&C Act section 736, and 70 FR 44106 (1 August 2005), an Application User Fee in the amount of \$767,400 has been paid for this application. The User Fee ID number for this NDA is PD3006213.

Submission Format

This NDA is in the International Conference on Harmonization (ICH) Common Technical Document (CTD) format, and is being filed electronically in accordance with Guidance for Industry - Providing Submissions in Electronic Format - NDAs (January 1999). The draft prescribing information (package insert) is in the Structured Product Labeling (XML-based) electronic format in accordance with Guidance for Industry - Submissions in Electronic Format - Content of Labeling (April 2005). This electronic submission format was reviewed and deemed acceptable for submission by the Division of Dermatologic and Dental Drug Products (DDDDP) at the Pre-NDA meeting between Connetics Corporation and DDDDP on 12 September 2005.

In accordance with FDA guidance, this NDA in CTD format has been created using PDF Version 1.4 and is optimally viewed using Adobe Acrobat 5.0 or 7.0. Acrobat 6.0 has a documented problem viewing hyperlinked pages optimally. In a teleconference with FDA electronic submissions representative Mr. Ken Edmunds (FDA/CDER/OBPS) on 16 November 2005, Mr. Edmunds advised Connetics that FDA is aware of the viewing problem with Adobe Acrobat versions 6.0 and that this problem has not been a refusal-to-file issue.

Sections of the CTD template that are not applicable to this NDA submission have been omitted; however, all applicable CTD sections included in this NDA retain their CTD-specified section numbering. Therefore, in some sections the section numbers will appear to "skip" over inapplicable section numbers. For example, when section 1.3 is not applicable but sections 1.2 and 1.4 are applicable, section 1.3 will not appear.

This NDA submission is provided in a CD-ROM format, with an approximate size of 300 megabytes. Connetics certifies that this electronic submission is virus-free. The submission was scanned by Symantec AntiVirus Corporate Edition version 8.0 prior to submission.

Right of Reference

To support the development and approval of this product, Connetics has obtained the right of reference to NDAs 17-010 and 17-426, Tridesilon Cream and Tridesilon Ointment, respectively, currently marketed by Perrigo, Inc., formerly Clay Park Labs, Inc. Connetics references the nonclinical and clinical safety data filed in NDAs 17-010 and 17-426 to augment the new data contained herein in support of Desonide Foam.

Stability Update

Reference is made to the Division's Pre-NDA meeting minutes dated 12 October 2005. Connetics notes that the Division agreed that a stability data update could be submitted during the NDA review period. This NDA includes comparability protocols for the use of an alternative manufacturing site and the introduction of new product sizes. These have been prepared according to FDA's draft guidance, "Comparability Protocols – Chemistry, Manufacturing and Controls Information" (February 2003).

Dosage Form

Connetics plans to initiate discussions with the CDER Nomenclature Committee in order to recommend greater opportunity for dosage differentiation under the "aerosol foam" dosage form definition in the CDER Data Standards Manual. Connetics believes that Desonide Foam should

be classified as an "emulsion foam" dosage form and is pursuing differentiating emulsion foams from other types of foam with different physical properties in the Data Standards Manual with the Nomenclature Committee. Currently, Desonide Foam would be classified as an "aerosol foam".

Proprietary Name

Connetics submitted the proprietary name ' — ' , and a backup name of "Verdeso", for FDA (DMETS) review in IND 67,825/SN0026 dated 1 November 2005.

Review Aids

In response to the Review Division's request, a Microsoft Word version of the draft prescribing information ("package insert") will be provided under separate cover as a "Review Aid - Not for Archive".

If you have any questions or comments on this submission, please contact me at 650.739.2614 or Zane Rogers, Senior Associate, Regulatory Affairs at 650.739.2908. The Regulatory Affairs facsimile number is 650.843.2802. Technical questions regarding this e-submission can be directed to Michael Barnotes, Regulatory Publisher, at 650.843.2804.

Sincerely,



Michael S. Eison, Ph.D.
Vice President, Regulatory Affairs

November 4, 2005

Clinical Review Comments for IND 67,825 SN 023

Based upon review of the spectroscopic analysis of Desonide foam and drug substance that showed minimal absorption in UVA, UVB and visible regions, the Agency agrees that dermal phototoxicity and photoallergenicity studies may be waived for this product when used for the indication sought.

APPEARS THIS WAY ON ORIGINAL

NOV-04-2005 11:24

FDA/CDER/DDDDP/HFD540

301 827 2091

P.03

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.


/s/

Felicia Curtis
11/4/2005 09:41:46 AM
CSO

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

**DEPARTMENT OF HEALTH AND HUMAN
SERVICES
FOOD AND DRUG ADMINISTRATION**
**PRESCRIPTION DRUG USER FEE
COVERSHEET**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS CONNETICS CORP Zane Rogers 3160 Porter Drive Palo Alto CA 94304 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 21978				
2. TELEPHONE NUMBER 650-7392908		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:				
3. PRODUCT NAME NA (Desonide Foam, 0.05%)		6. USER FEE I.D. NUMBER PD3006213				
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act </div> <div> <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY </div> </div>						
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO						
<p>Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <table border="0" style="width: 100%;"> <tr> <td style="width: 33%;">Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</td> <td style="width: 33%;">Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852</td> <td style="width: 33%;">An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</td> </tr> </table>				Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.				
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE Vice President, Regulatory Affairs	DATE 26 October 2005			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$767,400.00						
Form FDA 3397 (12/03)						

(IBE PRMT_CLOSE_G)

(Print Cover sheet)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-978

NDA ACKNOWLEDGMENT

Connetics
Attention: Michael S. Eison, Ph.D.
3160 Porter Drive
Palo Alto, CA 94304

Dear Dr. Eison:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Desonide Foam, 0.05%

Review Priority Classification: Standard (S)

Date of Application: November 18, 2005

Date of Receipt: November 21, 2005

Our Reference Number: NDA 21-978

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 20, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 21, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

NDA 21-978

Page 2

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Maria Anderson, Regulatory Project Manager, at (301) 796-1880

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisory Project Manager
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Maria Anderson
12/1/2005 11:29:37 AM
Signed for Mary Jean Kozma-Fornaro

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 12, 2005
TIME: 9:30 A.M.
LOCATION: S200A
APPLICATION: IND 67,825
DRUG NAME: Desonide foam 0.05%
TYPE OF MEETING: Pre-NDA meeting
MEETING CHAIR: Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
MEETING RECORDER: Shalini Jain/Regulatory Management Officer, DDDDP, HFD-540

FDA ATTENDEES:

Division of Dermatology and Dental Products

Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Ramesh Sood, Ph.D./Team Leader, Chemistry, DNDCIII, HFD-830
Steven Hathaway, Ph.D./Biostatistician, DBIII, HFD-725
Dennis Bashaw, Pharm.D./Team Leader, Clinical Pharmacology, DDDDP, HFD-540
Barbara Hill, Ph.D./Pharmacology Reviewer, DDDDP, HFD-540
Jill Lindstrom, M.D., Ph.D./Clinical Team Leader, Dermatology, DDDDP, HFD-540
Bindi Nikhar, Medical Officer, Dermatology, DDDDP, HFD-540
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII, HFD-725
Kathleen Fritsch, Ph.D./Biostatistics Reviewer, DBIII, HFD-725
Roy Blay/ DSI Reviewer, HFD-46
Margo Owens/Regulatory Management Officer, DDDDP, HFD-540
Shalini Jain/Regulatory Management Officer, DDDDP, HFD-540

EXTERNAL CONSTITUENT ATTENDEES:

Connectics Corporation

Diana Chen, M.D. / VP, Medical Affairs
Lincoln Krochmal, M.D. /EVP, Research & Product Development
Mark W. Davis, MS/ Senior Director, Clinical Operations & Project Team Leader
Alex Yaroshinsky, PhD. /VP of Clinical Operations and Biostatics
Wendy Chern, Ph.D. / VP, Research and Preclinical Development
Rebecca Mock, MBA/ Associate Director
Matt Foehr, B.S./Senior VP, Technical Operations
Michael Eison, Ph.D. /VP, Regulatory Affairs
Zane Rogers, Regulatory Affairs

MEETING OBJECTIVES:

To provide general guidance on the content and format of the proposed new Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document (submitted August 11, 2005) provides background and questions (page 6) for discussion.

Chemistry, Manufacturing and Controls:

Sponsor's Question:

1. Does the Agency agree with the proposed product specifications for Desonide Foam?
(Please see Table 7 in Section 13.2)

Agency's Response:

A test for Delivered Amount, per USP <601>, should be added to the specification. A control test for Leachable Impurities may also be needed (see Item 3 below). The proposed panel of tests would then be acceptable. The acceptability of the acceptance criteria is a review issue, and will be determined through review of the supporting data used to establish the proposed acceptance criteria.

Sponsor's Question:

2. Does the Division agree that the stability data described in Table 1 are adequate for NDA filing and to support a 24-month expiry date? (See Table 1 on page 7 of the pre-NDA briefing package)

Agency's Response:

The stability study bracket design appears to be acceptable. The proposed contents of the data package for submission and the planned data update during the review cycle are acceptable. Please note that if you propose an expiration dating period longer than the amount of real-time data available, then you should include a statistical analysis of the existing data to support such an extrapolated expiration dating period. The acceptability of the proposed 24-month expiration period is a review issue that will be determined during review of the data.

Sponsor's Question:

3. Does the Division agree with our plan for addressing potential leachables from the container-closure system?

Agency Response:

At this time, we cannot determine whether the plans described in Section 13.3 will lead to an acceptable correlation between leachable and extractable substances. As such, you should consider adding tentative tests and acceptance criteria for the identified leachates to the drug product specification. Once a valid correlation has been established between extracted and leached, you then could propose to delete the tests for leachates. From the cited guidance, "The identity and concentration of recurring leachables in the drug product or placebo formulation (i.e., drug product formulation without drug substance) should be determined through the end of the drug product's shelf life." You should have analytical results for the leachates through the projected expiration dating period, and the levels should be shown to be qualified via clinical exposures at maximal levels.

The sponsor stated that they would provide the nonclinical toxicology studies conducted to qualify the leachables (i.e., — and —) contained in the Desonide foam drug product in the NDA submission. The Division informed the sponsor that it would be acceptable to put these nonclinical toxicology studies in the CMC section of the electronic NDA submission with a link to the location of the studies in the Pharmacology/Toxicology section of the electronic NDA submission. The sponsor stated that they will provide information about the maximum level of clinical exposure to the leachables of Desonide foam in the NDA submission.

Pharmacology/Toxicology:

Sponsor's Questions:

1. Connetics has completed the toxicity studies recommended by the Division at the Pre-IND/End-of-Phase 2 Meeting held on 30 Mar 2004. Please see Section 12 for a summary of the nonclinical studies. Does the Division agree that the Connetics-sponsored non-clinical studies, along with the non-clinical information contained in NDAs 17-010, 17-426, and — (for Tridesilon Cream and Ointment, respectively) are adequate to support an NDA filing for Desonide Foam?

Agency's Response:

Inclusion of the Connetics-sponsored non-clinical studies along with the right of reference to the non-clinical information contained in the Tridesilon Cream and Ointment NDAs appears adequate for submission of the Desonide foam NDA. The fileability of an NDA is a review issue and will be determined after review of all of the submitted material to an NDA.

The sponsor clarified that the full study reports for the nonclinical toxicology studies conducted to support Tridesilon Cream and Ointment would not be included in the Desonide foam NDA submission. The Division stated that this would be acceptable as long as the sponsor includes the right of reference letter for Tridesilon Cream and Ointment in the NDA submission. The Division stated that it would be helpful if the sponsor provide a summary of the nonclinical toxicology studies conducted to support Tridesilon Cream and Ointment in the Desonide foam NDA submission.

The Division acknowledges that the sponsor has conducted an ICH battery of genetic toxicology studies for Desonide and sorbitan monolaurate (excipient) and will include the final study reports for these genetic toxicology studies in the Desonide foam NDA submission. The acceptability of these genetic toxicology studies to support the safety of Desonide foam will be determined after review of the final study reports.

The Division acknowledges that the sponsor states in the pre-NDA briefing package that they intend to study Desonide foam in a 2-year dermal carcinogenicity study in a single species and a photocarcinogenicity study in a single species as a post-marketing commitment. The Division requests that the sponsor include a timeline for conduct of both non-clinical post-marketing commitments in the Desonide foam NDA submission.

The sponsor stated that they will provide the requested timeline in the Desonide foam NDA.

Sponsor's Question:

2. Connetics plans to submit the full study reports for all Connetics-sponsored studies in the NDA. Results of the Connetics-sponsored non-clinical studies will be included in the Tabulated Summary. Non-clinical study reports for the Tridesilon products will be

cc:

DDDP/DIV DIR/WALKER
DDDP/PHARM SUP/BROWN
DDDP/PHARM/HILL
DDDP/MO/COOK
DPA II/CHEM/HOLBERT
DDDP/PM/BAUERLIEN

APPENDIX/ATTACHMENTS

Literature references

Goodwin, B.F., Creval, R.W., and Johnson, A.W. (1981). A comparison of three guinea pig procedures for the detection of 19 reported human contact sensitizers. Contact Dermatitis. 7: 248-258.

Hardin, B.D., Bond, G.P., Sikov, M.R., Andrew, F.D., Beliles, R.P., and Niemeier, R.W. (1981). Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work. Environ. Health 7: 66-75.

incorporated by reference (as authorized by the right-of-reference letter to Tridesilon NDAs 17-010 and 17-426 and [redacted] included in Appendix 5). Does the Division agree with the presentation format described above?

Agency's Response:

The sponsor's proposal for inclusion of the non-clinical toxicology information in the Desonide foam NDA submission appears acceptable from a pharmacology/toxicology perspective. It is requested that the summary table provided on page 19 of the Desonide foam pre-NDA briefing package (i.e., the list of non-clinical studies conducted under the Tridesilon cream and ointment NDAs) be included in the Desonide foam NDA submission.

Additional Pharmacology/Toxicology Comments from FDA:

The sponsor's proposal to electronically submit the Desonide foam NDA in the CTD format is acceptable from a pharmacology/toxicology perspective. The sponsor's proposal to submit the draft labeling for Desonide foam in the SPL electronic format is acceptable from a pharmacology/toxicology perspective. The sponsor's draft Table of Contents for the CTD NDA submission for Desonide foam is acceptable for submission of the NDA from a pharmacology/toxicology perspective. The fileability of an NDA is a review issue and will be determined after review of all of the submitted material to an NDA.

The Division has previously determined that a specification of [redacted] mole% for [redacted] in topical foam drug products that utilize a propane/butane propellant appears to ensure a level of [redacted] in the product that does not exceed a cancer risk of 1×10^{-6} , except in extreme scenarios. Therefore, the Division has determined that the specification of [redacted] mole% [redacted] for the propane/butane propellant used for Desonide foam, 0.05% would be acceptable. The sponsor specified the level of [redacted] in the propane/butane propellant for the Desonide foam, 0.05% drug product as NMT [redacted] ppm. It is not clear if this is equivalent to [redacted] mole% [redacted]. It is recommended that the sponsor assure that the level of [redacted] will be [redacted] mole% in the propane /butane propellant used for the Desonide foam, 0.05% drug product. It is requested that the sponsor provide the level of [redacted] in the propane/butane propellant used for the Desonide foam, 0.05% drug product in the NDA submission.

The sponsor stated that they will provide the requested information for [redacted] in the Desonide foam NDA.

Clinical Pharmacology and Biopharmaceutics:

Agency's Response:

While the meeting package does not contain any specific Clinical Pharmacology/Biopharmaceutic questions, we would like to comment on the fact that the two in vivo topical vasoconstrictor studies were done using the Office of Generic Drugs (OGD) multi-point assessment method. This is in contrast to the guidance given to the sponsor at the EOP2 meeting (page 33 of 79) where the single point methodology was agreed to by the sponsor. While the information will be supportive of their application, the sponsor should be aware that the Office of Clinical Pharmacology and Biopharmaceutics does not generally recommend the multi-point test, as it is used by OGD to assess the equivalence of dosage forms, something that the NDA side of the Agency does not accept this methodology for at this time. Ultimately, the acceptability of this data will be dependent on the proper bracketing of their foam formulation of Desonide for a relative potency determination.

Clinical:

Sponsor's Question:

1. Does the Division continue to agree that pending positive results, the clinical development program (described in Section 11.1) is adequate to support product approval for the proposed indication?

Agency's Response:

It is difficult to answer this question in absence of data from clinical trials.

The sponsor had been advised at the End-of-Phase 2 (EOP2) meeting on 3/30/04 that to obtain an indication of steroid-responsive dermatoses, studies would be required in patients with atopic dermatitis (AD) and psoriasis. However, since only patients with AD were included in clinical studies, the agency would like clarification that the indication sought by the sponsor is only mild-to-moderate AD.

At the EOP2 meeting, it was also discussed that the sponsor could choose one of the three agency suggested pathways for product approval; since the sponsor chose to perform only one pivotal Phase 3 study, results from this single study will have to be robust and persuasive for drug approval.

The sponsor should ask for a waiver of photosafety studies if spectrophotometric analysis of the final to be marketed formulation of their drug product showed no absorption in the 290-700nm range.

Sponsor's Question:

2. As discussed at the Pre-IND/EOP 2 meeting, a decision on whether a long-term safety study would be required will depend on safety results from clinical studies. Review of adverse event information from the Phase 2 study confirms that Desonide Foam is well tolerated and there does not appear to be treatment-related AEs that have not been previously reported for the active ingredient. If a similar safety profile of Desonide Foam is seen in the Phase 3 study, Connetics believes that a long-term safety study is not warranted. Does the Division agree? If the Division requires a long-term safety study for this product, Connetics requests that this requirement be satisfied as a post-marketing commitment.

Agency's Response:

Safety determination of a product is a review issue; the Division would like to review all safety information, including Hypothalamic Axis Suppression studies for Desonide foam before deciding that long-term studies are not warranted. In general, if reported AEs for Desonide foam are in keeping with similar AEs reported for the active product, then further long-term studies may not be required. If however, it is determined that long-term safety studies will be required, it is possible that these could be conducted as a post-marketing commitment. Please provide a comprehensive, worldwide, post-marketing safety report of all Desonide products.

Biostatistics:

Sponsor's Question :

1. Are the types of analyses planned for the primary and principle secondary efficacy endpoints in pivotal Phase 3 study DES.C.301 acceptable? Please see section 11.2 for the planned analyses.

Agency's Response:

The planned statistical analyses appear to be in agreement with the Division's recommendations at the End-of-Phase 2 (EOP2) Meeting and Special Protocol Assessment. The statistical analyses should follow the plan specified in the protocol. Regarding the pooling of small centers, the Division recommends developing a pooling algorithm for centers enrolling fewer than 8-10 subjects per treatment arm if the treatment allocation is 1:1. Since Study 301 involved randomization in a 2:1 ratio of Desonide to vehicle, the requirement for the minimum sample size on the vehicle arm before triggering pooling could be relaxed. This may help balance the need to minimize the impact of small cells with the desire to maintain the interpretation from individual centers whenever possible.

Sponsor's Question:

2. Does the Division agree that the structure of the NDA, as represented in the draft Table of Contents, is acceptable for NDA filing?

Agency's Response:

The Division would prefer that the Word copy of the draft labeling be of the non-annotated rather than the annotated version of the labeling.

Additional Biostatistics Comments from FDA:

The database for the Phase 2 and Phase 3 studies should include both raw variables (from the CRF) and derived variables suitable for conducting primary and secondary efficacy analyses (such as success on the IGA, and indicators for ITT and Per Protocol status, etc.) Each dataset should include the treatment assignments. The datasets should be submitted in SAS transport format. The submission should include adequate documentation for the datasets including definitions, formulas for derived variables, and decodes for any classification variables, so that all categories are well defined in the documentation.

In addition, the NDA submission should include the following items:

- a. study protocols, protocol amendments, and statistical analysis plans
The sponsor queried whether it was necessary to submit the statistical analysis plan document as all analyses are detailed in the protocol. The Agency responded that all formal documents describing the analyses should be submitted, however, it is not necessary to submit the shell tables.
- b. the randomization lists and the actual treatment allocations (with date of randomization) from the trials
- c. subgroup analyses by race, age, gender, and baseline severity
- d. complete description and a copy of the literature reference(s) for the discrete model data imputation method used in the sensitivity analysis

The sponsor stated that in addition to their Phase 3 study, the Phase 2 study they conducted also had positive results and they wondered what role this study might play. The Agency responded that findings from an adequately pre-specified and well-conducted Phase 2 study can supply

useful supportive information, depending on its design and results. The Agency will consider the complete body of evidence and each study on its merits, but does not modify phase designations of completed studies after the fact.

Electronic Submission Format/NDA Structure:

Sponsor's Question:

1. Connetics plans to submit the planned NDA in accordance with Guidance for Industry – Providing submission in Electronic Format – NDAs (January 1999). Connetics plans to electronically submit the planned NDA in the CTD format, as described in the 1999 Guidance document. The NDA will consist of files and comprehensive Tables of Content in the Adobe® PDF format. Does the Division concur that the submission format described above is acceptable for filing?

Agency's Response:

Yes, the Division concurs that an electronic submission of the NDA in the CTD format is acceptable, and the Adobe® PDF format for files and Table of Contents is acceptable for filing purposes.

Sponsor's Question:

2. Connetics plans to submit the draft labeling for Desonide foam in the SPL electronic format described in Guidance for Industry – Providing Submission in Electronic Format-Content of Labeling (April 2005), Section II, Part B, "New Technology for Processing Labeling and Labeling Changes." Does the Division find this acceptable?

Agency's Response:

Since per this Guidance document, it is the Agency's goal to complete the transition to Structured Product Labeling (SPL) by fall 2005, it would be acceptable for the sponsor to submit labeling in the SPL format. It is hoped that this form of labeling will help facilitate exchange of information between different health care information systems and will help overcome challenges posed by electronic labeling in PDF format.

Sponsor's Question:

3. Connetics plans to submit the NDA for Desonide foam in the CTD format. A draft Table of Contents is provided in Appendix 3. Does the Division agree that the structure of the NDA, as represented in the draft Table of Contents, is acceptable for NDA filing?

Agency's Response:

Yes, the draft Table of Contents in the CTD format is acceptable for NDA filing.

User Fee:

Sponsor's Question:

1. The NDA for Desonide Foam will be submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act (FD & C Act). In accordance with section 735 of the FD&C Act, an Application User Fee is required for 505(b)(1) applications. Accordingly, prior to year-end 2005, Connetics plans to submit an Application User Fee in the amount of \$767,400. Does the Agency concur that an Application User Fee is due, and that the proposed amount of the User Fee is correct?

Agency's Response:

Yes, the Agency concurs that an Application User Fee is due for fiscal year 2006, and that the proposed amount of \$767,400 is correct.

Administrative Comments

1. For applications submitted after February 2, 1999, the applicant is required to either certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
2. Comments shared with you today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or informational requests.
3. The sponsor is reminded of the Pediatric Research Equity Act of 2003, which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.
4. The sponsor is reminded to please submit appropriate patent certification at the time of NDA submission.

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/s/

Stanka Kukich

10/12/2005 08:41:58 AM

Sign off for Dr. Jonathan Wilkin, Division Director

JUL-11-2005 12:27

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P.02

July 11, 2005

IND 67,825--S-0019

Clinical Pharmacology/ Biopharmaceutics Comments:

In this submission, the sponsor has asked for clarification as to the need for in vivo biopharmaceutic trials for their 0.05% Desonide Foam. At the end of phase 2 (EOP2) meeting the sponsor agreed to conduct a single point vasoconstrictor study and an in vivo HPA axis suppression study in order to assess the in vivo bioavailability of their product. Since then the FDA has been asking sponsors to include in their development programs a direct assessment of the in vivo bioavailability using plasma sampling, as is done for other drug products. At the present time this is not a general requirement for all sponsors as it is unclear whether or not the analytical methods are yet sufficiently sensitive to move away from HPA axis assessment as a measure of in vivo bioavailability. As this sponsor was given guidance by the Agency at the EOP2 meeting to conduct the aforementioned vasoconstrictor and HPA axis studies, a direct assessment of in vivo bioavailability will not be required for this product.

The sponsor should be aware, however, that the Agency is, depending the availability of the technology, moving toward direct assessments of bioavailability through plasma sampling and that such a study may be requested for future products.

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Felicia Curtis
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 67,825/S-001

RECEIVED

JUL 14 2004

Connetics Corporation
Attention: Sharon L. Hall
Senior Director, Regulatory Affairs
3290 West Bayshore Road
Palo Alto, CA 94303

Dear Ms. Hall:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Desonide Foam, 0.05%.

We also refer to your May 20, 2004 submission, serial number 001, for a special clinical protocol assessment for the protocol entitled "A Phase 3, Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of Desonide Foam, 0.05% in the Treatment of Adolescent and Pediatric Subjects with Mild to Moderate Atopic Dermatitis".

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

Sponsor Question #1:

Does the Agency concur with the study design (subject population, study endpoints and study evaluations) of the Phase 3 study?

Agency Response:

Clinical

The Agency concurs with the study design, but has the following recommendations.

The Sponsor should include oozing/crusting as part of the IGA scale and the improvised IGA could read as follows:

0 = Clear; there may be minor residual discoloration; no erythema or induration/papulation, no oozing/crusting.

1 = Almost Clear; there may be trace faint pink erythema with almost no induration/papulation and no oozing/crusting

2 = Mild; there may be faint pink erythema with mild induration/papulation with no oozing/crusting

3 = Moderate; there may be pink-red erythema with moderate induration/papulation and there may be some oozing/crusting

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Page 2

4 = Severe; there may be deep or bright red erythema with severe induration/papulation with oozing/crusting.

Biostatistics

1. The sponsor has proposed conducting a single Phase 3, vehicle-controlled study. At the End of Phase 2 meeting held March 30, 2004, three development pathways were discussed: (1) two vehicle controlled trials, (2) one 3-arm study with desonide foam, vehicle, and another desonide comparator, and (3) one very persuasive, robust, highly significant, internally consistent vehicle controlled study. Protocol DES.C.301 is powered using a significance level of 0.05. If the results of this study do not meet all the criteria for a very persuasive study, then a second study with statistically significant results will be needed. If the sponsor elects to conduct only a single Phase 3 study, then they are strongly encouraged to power the study at a significance level substantially smaller than 0.05 or the study runs the risk of not being persuasive.

2. The sponsor is reminded that since no multiplicity adjustment for secondary endpoints has been proposed, the "additional evaluations" endpoints would not be considered for labeling purposes.

3. The sponsor may wish to consider randomizing patients in the Phase 2 study in a 1:1 ratio rather than 2:1 so that the success rates for the desonide and vehicle treatment arms are estimated with comparable precision, which may in turn increase the accuracy of the sample size calculation for the Phase 3 study.

Sponsor Question #2:

Does the Agency concur with the study enrollment criteria?

Agency Response:

Clinical

The study enrollment criteria seem reasonable, however the following changes are recommended. The Sponsor should include oozing/crusting as part of the enrollment criteria and the sum of the scores for erythema, induration/papulation and oozing/crusting should be at least 4 at study entry.

Sponsor Question #3:

Does the Agency concur with the planned statistical analyses?

Agency Response:

Clinical

The Agency concurs with the primary and secondary efficacy endpoints. Please refer to the recommended IGA scale. However, it is recommended that the Sponsor add the 3-week post treatment follow-up visit evaluations to the additional evaluation list.

IND 67,825
Page 3

Biostatistics

The sponsor plans to conduct a sensitivity analysis for the handling of missing data based on an article by Horton, Lipsitz, and Parzen (2003). Please provide additional details about this procedure in the protocol and submit a copy of the article with any revisions to this protocol.

In addition, the following comments are provided:

Clinical

1. At the March 30, 2004 Pre IND/End of Phase 2 meeting, the Sponsor was advised that Phase 2 dose ranging studies be conducted prior to Phase 3 studies. However, this Phase 2 study is to be conducted concurrently with the submitted Phase 3 study and the sample size for the Phase 3 study may be increased depending on results from the Phase 2 study.

The Division reiterates its previous comments (stated at the Pre-IND/End of Phase 2 meeting) regarding one out of 3 study design pathways that could be followed for drug approval. Since the Sponsor is choosing to perform one double-blind vehicle controlled study, a second study may be required if results from this study are not persuasive or robust. Please also refer to the Biostatistical comments for Question #1.

2. Patients should be given a list of permissible emollient products to choose from and should be allowed to use emollients on areas of atopic dermatitis in between study drug applications, since this would mimic clinical practice.

3. It is noted that you are seeking atopic dermatitis as the indication, and not "corticosteroid responsive dermatoses".

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Ginny Giroux, Regulatory Health Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

IND 67,825

Page 4

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/s/

Jonathan Wilkin
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FDA Fax Memo

Date: June 2, 2004

Subject: IND 67,825/Desonide Foam, 0.05%

Dear Ms. Hall,

The Clinical reviewer requested that the following comments, related to Protocol No. DES.C.201 (HPA Axis Suppression Study), be conveyed to you:

1. The protocol indicates that Cortrosyn will be administered either intravenously or by intramuscular injection. As far as is possible, only one route of administration should be used for each subject.
2. The criterion to establish a normal response to Cortrosyn was incorrectly stated by the Agency at the pre-IND/end-of-phase 2 meeting to be a post-injection serum cortisol level of $\geq 18 \mu\text{g/dL}$ obtained 30 minutes after Cortrosyn administration. This should be corrected to a post-injection serum cortisol level of $> 18 \mu\text{g/dL}$ obtained 30 minutes after Cortrosyn administration.
3. At the screening visit, the criterion to establish a normal response to Cortrosyn should be changed from a post-injection serum cortisol level of $\geq 18 \mu\text{g/dL}$ obtained 30 minutes after Cortrosyn administration, to a post-injection serum cortisol level of $> 18 \mu\text{g/dL}$ obtained 30 minutes after Cortrosyn administration. It is important that patients show a post-injection cortisol level of $> 18 \mu\text{g/dL}$ obtained 30 minutes after Cortrosyn administration to be considered eligible for the study.
4. Pregnancy testing is scheduled for the screening, week 4 and conditional visits. Because Cortrosyn is pregnancy category C, females of child-bearing potential should have the pregnancy test confirmed to be negative prior to the administration of Cortrosyn at these visits.
5. Patients using systemic immunomodulators including biologic agents should be excluded from the study.
6. In addition to erythema and scaling, the degree of lichenification should be incorporated into the Investigator's Static Global Assessment for grading disease severity.
7. The Sponsor should submit the name and address of the laboratory used along with laboratory reference values for baseline cortisol concentrations (and stimulated concentrations, if listed).
8. Clinical Pharmacology/Biopharmaceutics comments may be communicated separately.

If you have questions, please call.

Respectfully,

Ginny Giroux

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/s/

Virginia Giroux
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PIND 67,825
3/30/04
PIND/EP2meeting

MEMORANDUM OF MEETING MINUTES

Meeting Date: March 30, 2004 **Time:** 10:00

Location: S200A **Meeting ID:** 12457

Topic: PIND 67,825, Desonide Foam 0.05% for inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

Subject: Pre-IND/EP2 meeting

Sponsor: Connetics Corporation

Meeting Chair: Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540

Meeting Recorder: Ginny Giroux/Regulatory Management Officer, DDDDP, HFD-540

FDA Attendees:

Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
 Stanka Kukich, M.D./Deputy Division Director, DDDDP, HFD-540
 Terri Rumble, R.N., B.S.N./Associate Director of Regulatory Affairs, ODE V, HFD-105
 Markham Luke, M.D., Ph.D./Team Leader, Clinical, Dermatology, DDDDP, HFD-540
 Joseph Porres, M.D./Clinical Reviewer, DDDDP, HFD-540
 Paul Brown, Ph.D./Pharmacology Reviewer, DDDDP, HFD-540
 Joel S. Hathaway, Ph.D./Chemistry Reviewer, DNDCIII, HFD-830
 Kathleen Fritsch, Ph.D./Biostatistician, DBIII, HFD-725
 Abi Adebawle, Ph.D./Pharmacokinetics Reviewer, DPEIII, HFD-880
 Leonthena Carrington/Regulatory Project Manager, DDDDP, HFD-540
 Ginny Giroux/Regulatory Project Manager, DDDDP, HFD-540

Sponsor Attendees:Connetics

Charles DeMocko, Vice President, Regulatory Affairs
 Zane Rogers, Associate, Regulatory Affairs
 Prema Vijayakumar, M.S., Director, Process Development & Non-Commercial Contract Manufacturing
 Gary Miller, M.S., Associate Director, Analytical Development
 Lincoln Krochmal, M.D., Executive Vice President, Research & Product Development
 Xinfan Huang, M.D., Senior Director, Nonclinical Research & Development
 Dave Dimmick, Vice President, Quality
 Judith Myers, Director, Clinical Operations
 Alex Yaroshinsky, Ph.D., Vice President, Biostatistics and Clinical Operations

Purpose:

To provide general guidance on the content and format of the proposed new Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document (submitted February 27, 2004) provides background and questions (p 4-9) for discussion. The sponsor requests discussion on the clinical program, nonclinical plan, and chemistry, manufacturing, and control supporting data required for approval of Desonide Foam.

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PIND 67,825

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PIND/EP2meeting

Chemistry, Manufacturing and Controls:**Sponsor's Question 1:**

Does the Agency agree that the proposed product testing program (Release and Stability) as described in this briefing document are sufficient for (1) initiating the clinical development program, and (2) evaluating the product to support approval?

Agency's Response:

- (1) Yes. The sponsor appears to have sufficient information available to submit the proposed IND.
(2) The assessment of the adequacy of data submitted is a review issue.

Sponsor's Question 2:

Does the Agency agree that the proposed extraction study design is acceptable for product approval?

Agency's Response:

Yes. The extraction study design is acceptable.

In addition, we have the following comments regarding the submission of CMC information in the IND:

1. Please refer to the FDA guidance document, "Guidance for Industry, INDs for Phase 2 and Phase 3 Studies - Chemistry, Manufacturing, and Controls Information," for the scope of information that is expected to be submitted in the IND. The development of manufacturing, packaging and controls procedures is expected to be well established prior to embarking on Phase 3 clinical studies; any significant changes to CMC information during Phase 3 might have an impact on the acceptability of that information in future submissions.
2. It would be advisable to establish an in-process control at the end of step 4 of the manufacturing process (page 48 of the briefing) to assure complete dissolution of the drug substance.

Discussion during the meeting:

The Sponsor noted that an in-process control will be implemented for the indicated manufacturing step.

3. The composition of the can liner material should be disclosed either in the IND or in a DMF. It is expected that the sponsor can demonstrate that the extraction study and the analytical methods will be able to show that they are capable of detecting the components of the _____ liner.

Discussion during the meeting:

The Sponsor indicated that the composition of the can liners would be submitted in the IND, and that the extraction study results would be submitted in the NDA.

4. It is not clear that the Leakage and Weight Loss tests in the proposed drug product specification are evaluating different quality attributes. Also, it appears that results of these tests presented in the stability data (pages 60-62) are not being calculated correctly. The results seem to indicate _____ the acceptance limits should also be established without reference to time limits, e.g. "Weight Loss NMT _____ % per year" should rather be expressed as "Weight Loss NMT x.x%". The maximum weight loss should be supported by the data collected during the stability studies.

Discussion during the meeting:

The Sponsor indicated that the Leakage test was a release test, while the Weight Loss test was a stability test. They also clarified that the test measures a rate of weight loss, with a typical package showing the greatest

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Reviewer comment: The rationale and results for the "weight loss rate" test are not clear. It does not seem that the rate of weight loss, especially such low observed rates, would lead to useful results over the shelf-life of the product, while the measurement of absolute weight loss, compared against a static acceptance limit, is much easier to interpret for its regulatory utility.

The Sponsor proposed to explain and clarify the rationale and interpretation of this test and its results.

5. The drug product specification's test for related substances should also include limits for unknown substances. Refer to the ICH guidance document, "Guidance for Industry - Q3B(R) Impurities in New Drug Products."

Discussion during the meeting:

The Sponsor indicated that they will include this in the IND.

6. The UV spectrum of drug substance (Figure 2, page 58) was determined on a sample that appears to be too dilute. While this concentration is similar to the concentration of drug substance in the product's spectrum (Figure 1), it is not adequate for the assessment of the wavelengths at which the drug substance absorbs. Please provide a UV spectrum with greater absolute absorption so that we can assess the full spectrum (200-700 nm) of the active.

Discussion during the meeting:

The Sponsor indicated that they will provide a UV spectrum using conditions to achieve a maximum absorption of approximately 1AU. This was acceptable per the FDA chemist.

7. Please be aware that the issues of dispensable amounts in the physician's sample package, pertaining to the other Connetics foam products, should also be addressed for this product as well.
8. The formulation statement should include the quantities of propellant for each package size. This may be provided as an additional column in Table 8.

Discussion during the meeting:

The Sponsor discussed their plan for documenting the amount of propellant in a section separate from the quantitative composition. The FDA chemist advised the Sponsor that the propellant is considered part of the formulation, and should be identified and controlled as such.

Pharmacology/Toxicology:

Sponsor's Question:

Does the Agency agree that the proposed nonclinical development program is sufficient for initiation of clinical studies and product approval?

Agency's Response:

The proposed nonclinical development program (e.g., dermal and eye irritation studies in rabbits and a dermal sensitization study in guinea pigs) is sufficient for initiation of clinical studies with desonide foam, 0.05% but is not sufficient for approval of desonide foam, 0.05%. Additional nonclinical studies recommended for the approval of desonide foam, 0.05% are listed below.

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1. Several corticosteroids have been shown to be genotoxic. The genotoxicity of desonide has not been characterized. It is recommended that the standard ICH battery of genotoxicity tests be conducted to support an NDA (refer to ICH Guidances S2A, Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals and S2B, Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals tests). Full published literature reports might be appropriate to fulfill some of this requirement if they are deemed adequate upon review.
2. The division has determined that treatment of corticosteroid dermatoses is a chronic indication. Therefore, a nonclinical dermal carcinogenicity study and a study to determine the photoco-carcinogenic potential of desonide foam, 0.05% are recommended as phase 4 commitments. The sponsor is referred to the existing ICH guidelines (ICH-S1A, ICH-S1B, ICH-S1C, ICH-S1C(R)) and CDER guidance for industry (Carcinogenicity study protocol submissions) that discuss recommendations for conduct of carcinogenicity studies. In addition, the sponsor is referred to the CDER guidance for industry (Photosafety testing) that discusses recommendations for conduct of studies to determine the photoco-carcinogenic potential of a topical drug product.

Discussion during the meeting:

During the meeting it was clarified that a single dermal carcinogenicity study in rat or mouse was recommended. The Agency would consider a proposal to conduct a study in a transgenic model. In addition, it was clarified that a single study of photocarcinogenic potential would probably be adequate and that the sponsor could propose a model for this study. The evaluation of the photocarcinogenic potential was recommended regardless of the UV/Vis absorption properties of the drug product.

3. Inadequate data was contained in the literature reference article submitted to support the sorbitan monolaurate excipient. The following data gap was identified for sorbitan monolaurate.
 - a. No genetic toxicology studies conducted with sorbitan monolaurate were described in the literature reference. It is recommended that the standard ICH battery of genotoxicity tests be conducted with sorbitan monolaurate to support an NDA (refer to ICH Guidances S2A, Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals and S2B, Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals tests). Full published literature reports might be appropriate to fulfill some of this requirement if they are deemed adequate upon review.

Discussion during the meeting:

The sponsor agreed to provide the ICH battery of genotoxicity information for desonide and sorbitan monolaurate.

Additional Pharmacology/Toxicology comments:

1. The need for a nonclinical photoirritation study may be waived for desonide foam, 0.05% if no absorption is noted in the UVA/UVB/VIS spectrum (290 nm – 700 nm) obtained with a higher concentration of the drug substance and all the excipients, either individually or together. It is requested that the sponsor include all of the UVA/UVB/VIS absorption spectra with the IND submission for desonide foam, 0.05%.
2. It is requested that the sponsor include the right of reference letter for NDAs 17-010 and 17-426, Tridesilon cream and Tridesilon ointment, with the IND submission.
3. The results of the studies described in the reference article titled "Final Report on the Safety Assessment of Phenoxyethanol" appear to be adequate to qualify use of the phenoxyethanol excipient in the desonide foam, 0.05%. It is recommended that the sponsor include this literature reference article in the IND submission for desonide foam, 0.05%.

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PIND 67,825
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4. The level of _____ contained in the butane/propane propellant was not specified in the briefing package. It is recommended that this information be provided in the IND submission.

Discussion during the meeting:

The sponsor agreed to provide the information requested in the additional comments 2-3 above.

Biopharmaceutics:

No Biopharm questions were identified in the briefing document. The Agency has the following comments:

With regards to the in vivo biopharmaceutic aspects of this application, the sponsor will need to undertake a Single-Point topical vasoconstrictor study. The study should evaluate the vasoconstrictor (skin blanching) properties of their re-formulated product vs. the original product and appropriate reference products such as hydrocortisone to allow for bracketing to determine relative potency via this assay.

As for the HPA axis trial, the study design is in general acceptable, however, the sponsor needs to refine their trial in that the blood sample for the characterization of plasma cortisol levels should be obtained at 30min and not between 30 to 60min after IV dosing as proposed in the protocol. In addition the sponsor should record the degree of involved skin at study entry and at the final study visit.

Additional clinical comments will be provided by the reviewing medical officer.

Discussion during the meeting:

The Sponsor confirmed they will do a Single-Point topical vasoconstrictor study and follow the Agency's recommendations for the HPA axis trial.

Clinical:

Sponsor's Question 1:

Does the Agency agree that the scope and timing of the clinical development program, in addition to the data contained in NDAs 17-010 and 17-426 (Tridesilon Cream and Ointment, respectively) is sufficient to support product approval for the proposed indication?

Agency's Response:

To fully be able to use the Tridesilon database, the Sponsor would need to provide a bridging clinical study including the comparator. Please refer to CFR 21.320-24(b)(4), Types of Evidence to Measure Bioequivalence or Establish Bioequivalence.

To obtain the indication steroid-responsive dermatosis, traditionally studies in atopic dermatitis and in psoriasis have been required. The Sponsor may suggest other indications to study if the Sponsor does not wish to study psoriasis. Labeling could be designed to include the indications for which safety and efficacy are demonstrated.

For eventual drug approval for each indication, one of the following pathways could be followed:

- a) Two independent, double-blind, vehicle controlled studies demonstrating superiority to vehicle.
- b) One 3-arm (desonide foam, desonide foam vehicle, and comparator desonide active) study demonstrating superiority of desonide foam to its vehicle and non-inferiority to the comparator. A fourth small comparator vehicle-like arm is recommended for blinding purposes.
- c) One very persuasive, robust, double-blind, vehicle controlled study demonstrating superiority to vehicle. The study should be highly statistically significant with no major flaws and consistent results across centers and subgroups.

Further comments are provided later on regarding the proposed indication.

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PIND 67,825
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PIND/EP2meeting

Sponsor's Question 2:

Does the Agency agree with the design (subject population, study endpoints, and study evaluations) of the proposed clinical studies?

Agency's Response:

1. It is difficult to have agreement with protocols submitted in synopsis form. Please submit the final protocols as an SPA for review.
2. Topical safety studies in humans, with the to-be-marketed formulation, will be needed for drug approval. These include cumulative irritancy and sensitization, photosensitivity and photoallergenicity studies. The latter two might be waived if sponsor can show the to-be-marketed product, or all of its ingredients, do not absorb light in the 280-700 nm range.
 - 2.1 The submitted protocol for irritancy and sensitization, DES.C.102, seems to generally follow the usual protocol for this type of study but it includes testing of only vehicles; it should include the study drug and its vehicle.
3. HPA axis suppression. The following are comments on the proposed study, DES.C.201:
 - 3.1 It is recommended that all age groups be studied simultaneously and that adequate numbers of patients are enrolled for each age group.
 - 3.2 The Agency is currently using, as the sole criterion to establish a normal response, the post-injection serum cortisol level of 18 µg/dl or greater. The serum or plasma cortisol level should be drawn 30 minutes after administration of the Cortrosyn.
 - 3.3 It is recommended that the age groups to be included in an HPA axis suppression study be as follows:

12-18 years old
6-12 years old
3- 6 years old
3 months to 3 years old.

- 3.4 It is recommended that for enrollment patients be required to have a minimum of 25% body surface area involvement.
- 3.5 The HPA axis suppression study could be run concurrently with Phase 3 pivotal trials.
4. Vasoconstriction study should be a bracketed single-point Stoughton-McKenzie assay. See also, Biopharm comments.
5. Safety and efficacy studies. You are proposing protocol DES.C.301. The following are comments on this protocol:
 - 5.1 Inclusion/exclusion criteria.
 - 5.1.2 To facilitate the demonstration of efficacy, it is recommended that for study entry a minimum score be required for each of the following: erythema, induration, and oozing/crusting. No subject should be enrolled that could be defined as success at baseline. The Sponsor is proposing to enroll patients with mild-to-moderate (IGA=2-3) atopic dermatitis. It is recommended that for study entry the sum of the scores for erythema, scaling, induration/papulation, and lichenification should be at least 4.
 - 5.1.3 The protocol calls for the exclusion of patients who have used antihistamines within a week. This exclusion may be inappropriate because patients with atopic dermatitis classically present with marked pruritus. It is recommended that patients who have not changed the antihistamine dose for at least 2 weeks be permitted enrollment.
 - 5.2 Assessment scales. It is recommended that, to declare success in a patient, a change from baseline in IGA of at least 2 steps (from 3 to 1, or from 2 to 0) be required. This grading system would facilitate distinguishing the effect of active versus vehicle. There should be some clinical correlation between IGA level and signs and symptoms, so that patients whose IGA at the assessment time are declared as "success," have a total score of

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signs and symptoms that is also very low. The signs and symptoms to monitor in the study should include erythema, scaliness, induration/papulation, oozing/crusting, lichenification and pruritus. The Sponsor may submit plans detailing which signs and symptoms to include as primary or secondary endpoints, based on the expected activity of the proposed drug product.

5.3 Assessment time. You are proposing to stop treatment of patients when they reach an IGA score of 0-1 and a erythema and scaling score of 0-1, and to classify them as "success." It is recommended that all patients are evaluated at a pre-specified time-point. If these patients, whose treatment was discontinued because of early resolution of atopic dermatitis, worsen by the assessment time-point, they could not be considered "success."

5.4 Toiletries. On page 180 it is stated the Sponsor will provide patients with a cleanser and a bland emollient. It is recommended that patients be allowed to use their routine toiletries, or be provided a list of permissible products. Alternatively the study could be designed to assess the effect on safety and efficacy of any products that are provided.

Additional comment:

The Sponsor plans to conduct dose-ranging studies concurrently with the pivotal trials. It is recommended to conduct dose-ranging studies prior to conducting Phase 3 trials. Dose-ranging studies usually include drug concentration, frequency of application and duration of treatment and enable the selection of the dosage showing the optimal safety and efficacy, and to estimate sample size for Phase 3 trials.

Sponsor's Question 3:

Does the Agency concur with the proposal to enroll subjects in a given age cohort into the Phase 3 study after safety with respect to HPA axis suppression for that age cohort is established in the Phase 2 study?

Agency's Response:

The Agency recommends that patients of all ages be enrolled at the same time from the start, and that adequate numbers of patients from each age group be enrolled. The Sponsor may enrich for younger children to assess for safety.

Sponsor's Question 4:

Does the Agency agree that the proposed safety database for Desonide Foam (approximately 477 subjects) will be sufficient to support product approval, provided no unanticipated safety issues arise other than those noted in the Tridesilon Cream and Ointment product Labeling?

Agency's Response:

Please assess and address the long-term safety for this product as per ICHE1a.

Discussion during the meeting:

The Sponsor inquired during the meeting about the number of patients to be included. This number will depend on whether a safety signal develops during the studies and will be a review issue.

Biostatistics:

Sponsor's Question 1:

Does the Agency concur with the primary and secondary statistical analyses outlined in the Phase 3 protocol (DES.C.301, Attachment 8)?

Agency's Response:

1. The primary endpoint is defined two ways in the protocol
 - (a) ISGA ≤ 1 , scaling ≤ 1 , erythema ≤ 1 (Section 1)
 - (b) ISGA ≤ 1 , scaling ≤ 1 , erythema ≤ 1 , pruritus ≤ 1 (Section 7.4.1).
- Refer to the clinical comments for the recommended definition of the primary efficacy endpoint.

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Discussion during the meeting:

The sponsor noted that the inclusion of pruritus in the definition of the endpoint in Section 7.4.1 was unintentional.

2. The protocol specifies LOCF as the primary method for imputing missing data. To ensure that the efficacy results are not influenced by the method of data imputation, a sensitivity analysis using an alternate method of data imputation should also be planned in the protocol as a secondary analysis to assess the effect of data imputation. This analysis would be in addition to the per protocol analysis.

Sponsor's Question 2:

An interim analysis will be performed in the Phase 3 Study (DES.C.301) to verify the assumption underlying sample size and power calculations. That is, only the primary efficacy endpoint will be evaluated after approximately 50% of subjects are enrolled and treated for 4 weeks. To account for efficacy assessments at the time of the interim analysis, the significance level for final analysis will be adjusted according to the methodology described in the article by Fleming, et al (Appendix 2). The adjusted significance level will be equal to 0.04806. Does the Agency concur with this statistical methodology?

Agency's Response:

The Agency recommends conducting a Phase 2 trial to estimate the treatment effects, which then can be used to adequately power Phase 3 trials. In this case no interim analysis to recalculate the sample size would be needed in the Phase 3 trial.

If the sponsor chooses to retain an interim analysis in Study DES.C.301, the following should be considered:

1. The methodology for the interim analysis should be appropriate for the goals of the interim analysis. The protocol states that the goal of the proposed interim analysis is to recalculate the sample size. The proposed methodology by Fleming, *et al* does not appear to address the issue of sample size recalculation, as the method is only designed to permit early stopping for higher than expected efficacy. If the goal of the interim analysis is sample size recalculation, then the protocol should specify a methodology for this purpose with full details of the procedure.
2. The charter for the Independent Interim Analysis Committee should be developed before the study is initiated. The charter should detail how data for the interim analysis will be handled and how appropriate firewalls between the committee and personnel involved in the conduct of the study will be maintained.

Administrative Comments

1. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
2. The Sponsor is encouraged to submit its revised protocols for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses as Special Protocols through the 45-day Special Protocol Assessment (SPA) mechanism for Agency review, comment and agreement, prior to study initiation.
3. Your pre-IND has been assigned IND 67,825. Please reference this number on all submissions and correspondence.

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/s/

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/s/

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-978	Efficacy Supplement Type SE-N/A	Supplement Number N/A
Drug: — (desonide) Foam, 0.05%		Applicant: Connetics Corporation
RPM: Melinda Bauerlien, M.S.		HFD-540 Phone # 301-796-2110
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>N/A</p>
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		September 21, 2006
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number PD3006213
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify) N/A
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify) N/A
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

• This application is on the AIP	<input type="radio"/> Yes <input checked="" type="radio"/> No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input checked="" type="radio"/> Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="radio"/> Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) <input type="radio"/> Verified N/A 21 CFR 314.50(i)(1) <input type="radio"/> (ii) <input type="radio"/> (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	N/A
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i>	<input type="radio"/> N/A (no paragraph IV certification) <input type="radio"/> Verified N/A
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.	
Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?	<input type="radio"/> Yes <input type="radio"/> No
(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).	N/A
If "Yes," skip to question (4) below. If "No," continue with question (2).	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	<input type="radio"/> Yes <input type="radio"/> No N/A
If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).	
If "No," continue with question (3).	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	<input type="radio"/> Yes <input type="radio"/> No N/A

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

() Yes () No

N/A

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

() Yes () No

N/A

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	N/A
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ () No N/A
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	

❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	September 18, 2006
• Most recent applicant-proposed labeling	N/A
• Original applicant-proposed labeling	November 18, 2005
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	September 13, 2006 DMETS; August 15, 2006 DDMAC
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	November 18, 2005
• Reviews	September 13 and 18, 2006 DMETS; August 15, 2006 DDMAC
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	September 7, 2006
• Documentation of discussions and/or agreements relating to post-marketing commitments	September 11, 2006
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	March 30, 2004
• Pre-NDA meeting (indicate date)	September 12, 2005
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (<i>indicate date for each review</i>)	September 19, 2006
❖ Clinical review(s) (<i>indicate date for each review</i>)	September 8, 2006
❖ Microbiology (efficacy) review(s) (<i>indicate date for each review</i>)	N/A
❖ Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>)	September 8, 2006
❖ Risk Management Plan review(s) (<i>indicate date/location if incorporated in another rev</i>)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	September 19, 2006
❖ Demographic Worksheet (<i>NME approvals only</i>)	N/A
❖ Statistical review(s) (<i>indicate date for each review</i>)	June 21, 2006
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>)	April 21, 2006
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
❖ CMC review(s) (<i>indicate date for each review</i>)	September 7, 2006
❖ Environmental Assessment	
• Categorical Exclusion (<i>indicate review date</i>)	September 7, 2006
• Review & FONSI (<i>indicate date of review</i>)	September 7, 2006
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	September 7, 2006
❖ Microbiology (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	N/A
❖ Facilities inspection (provide EER report)	Date completed: September 6, 2006 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed () Requested () Not yet requested
Nonclinical Section / Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	July 13, 2006
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	June 21, 2006
❖ CAC/ECAC report	N/A